

**Cyclisation / Desymmetrisation Reactions  
of  
Cyclohexa-1,4-Dienes**

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**A Thesis Submitted for the Degree of  
Doctor of Philosophy**

**at**

**Cardiff University**

**July 2006**

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## Abstract

This thesis describes different strategies to desymmetrise 1,4-cyclohexadiene derivatives with concomitant formation of a quaternary stereogenic centre.

Chapter 1 gives a brief overview of the previous desymmetrisation and diastereotopic group selection processes of 1,4-cyclohexadiene derivatives.

Chapter 2 describes the initial model studies for the formation of the quaternary stereogenic centre using achiral cyclohexa-1,4-dienone derivatives. This was developed to permit stereoselective formation of a quaternary stereogenic centre using a chiral sulfinyl group as the stereodirecting influence during the cyclisation step. This proceeded with acceptable levels of discrimination between the two diastereotopic double bonds.

Chapter 3 outlines attempts to improve the level of diastereoselectivity obtained under the influence of the sulfinyl group by synthesising a range of different compounds having only carbon atoms in the tether.

Chapter 4 describes the desymmetrisation of the two diastereotopic double bonds of derivatives of cyclohexa-1,4-diene using free-radical methodology. The sense and level of the diastereoselectivity is dependent on the protecting group used. Application of this methodology toward natural product synthesis has been described.

Chapter 5 describes the desymmetrisation of the two diastereotopic double bonds of 1,4-cyclohexadiene derivatives using the Prins cyclisation reaction. This approach afforded an easy and stereocontrolled access to fused tetrahydropyrans and tetrahydrofurans depending on the reaction conditions employed. The stereochemical outcome of all of these reactions can be rationalised by a single transition state model.



## Acknowledgements

There are so many people that I have to thank for helping me over the past three years. First of all my greatest thanks go to Dr Mark Elliott for his help, continued guidance and for being patient with me also for showing me the way in the early days. I'm very grateful for him for his unlimited help and for making me understand stereochemistry. I am grateful to Dr David Kelly for his direction during mentoring meetings and to his group for allowing me to attend their group meetings. Thanks to Professor David Knight and Dr Mike Coogan for their help.

I would like to acknowledge all the past and the present members of lab 1.107; in particular Stuart for all the help and advice he has given me.

I would like also to thank all the technical staff in chemistry department at Cardiff university specially Dr Li-Ling Ooi for the X-ray crystallography data, Rob and Robin for help with mass spectrometric analysis and for Terrie for being nice to me. I am grateful to the staff at the EPSRC National Mass Spectrometry Service, Swansea for high resolution mass spectrometric data.

I would like to express my thanks to my father who gave me the strength to continue, my brothers and sisters and aunt Amal for being supportive. Finally I'm very grateful to my country The Arab Republic of Egypt for giving me this great opportunity and I would like to thank Professor Abdulla M. Molokhia and Professor Mohamed Badawy for their help in applying for this grant.

## **Dedication**

*This work is dedicated to the memory of my mother who was always there for me.*

# Table of Contents

<b>Title Page</b>	<b>i</b>
<b>Declaration</b>	<b>ii</b>
<b>Abstract</b>	<b>iii</b>
<b>Acknowledgements</b>	<b>iv</b>
<b>Dedication</b>	<b>v</b>
<b>Table of Contents</b>	<b>vi</b>
<b>Detailed Table of Contents</b>	<b>vii</b>
<b>Abbreviations</b>	<b>x</b>
<b>Chapter 1. Introduction</b>	<b>1</b>
<b>Chapter 2. Desymmetrisation Strategies – A Starting Point</b>	<b>30</b>
<b>Chapter 3. Desymmetrisation Strategies – Further Studies</b>	<b>63</b>
<b>Chapter 4. Diastereoselective Free-radical Cyclisation Reactions of Cyclohexa-1,4-dienes</b>	<b>91</b>
<b>Chapter 5. Lewis Acid-promoted Diastereoselective Prins Reactions of Cyclohexa-1,4-dienes</b>	<b>110</b>
<b>Chapter 6. Experimental Section</b>	<b>152</b>
<b>Appendix A. Compound List</b>	<b>273</b>
<b>Appendix B. Crystallographic Data</b>	<b>281</b>
<b>Appendix C. <sup>1</sup>H NMR Spectra of Selected Compounds</b>	<b>303</b>
<b>References</b>	<b>310</b>

## Detailed Table of Contents

<b>Title Page</b>	i
<b>Declaration</b>	ii
<b>Abstract</b>	iii
<b>Acknowledgements</b>	iv
<b>Contents</b>	v
<b>Detailed Table of Contents</b>	vi
<b>Abbreviations</b>	x
<b>Chapter 1. Introduction</b>	<b>1</b>
1.1. Background to the project	2
1.2. Differentiation approaches that occur during a cyclisation step	3
1.3. Enantioselection approaches before any cyclisation reaction	7
1.4 Previous desymmetrisation reactions of cyclohexadienes	8
1.4.1. Diastereotopic group selection	8
1.4.1.1. Desymmetrisation approaches of cyclohexadienes having the stereogenic centre within the tether	8
1.4.1.1.1. Cycloaddition reactions	8
1.4.1.1.2. Conjugate addition reactions	10
1.4.1.1.3. Free-radical reactions	15

1.4.1.2. Desymmetrisation approaches of cyclohexadienes having the stereogenic centre outside the tether	18
1.4.2. Enantiotopic group selection	21
1.4.3. Application of chiral metalated cyclohexadiene complexes in asymmetric synthesis	28
<b>Chapter 2. Desymmetrisation Strategies – A Starting Point</b>	<b>30</b>
2.1. Introduction	31
2.2. Synthesis and cyclisation of achiral precursors	31
2.3. Synthesis and cyclisation of chiral sulfoxide precursors	39
2.4. Synthesis of amide substrates for cyclisation	53
2.5. Conclusion	62
<b>Chapter 3. Desymmetrisation Strategies – Further Studies</b>	<b>63</b>
3.1. Introduction	64
3.2. Synthesis of carbon-tether precursors	65
3.3. Alkylation of methyl 1,4-dihydrobenzoate	69
3.4. Further studies towards substrate synthesis	71
3.5. Conclusion	89
<b>Chapter 4. Diastereoselective free-radical cyclisation reactions of cyclohexa-1,4-dienes</b>	<b>91</b>
4.1. Cyclisation reactions of aryl radicals	92

4.2. Diastereoselective free-radical cyclisation reactions	98
4.3. Assignment of the stereochemistry of the cyclisation products	102
4.4. Discussion of the stereochemical outcome of the free radical cyclisation reactions of 1,4-cyclohexadiene derivatives	103
4.5. Application of radical reactions to lycoposerramine A	105
 <b>Chapter 5. Lewis acid-promoted diastereoselective Prins reactions of cyclohexa-1,4-dienes</b>	 <b>110</b>
5.1. Introduction	111
 <b>Chapter 6. Experimental section</b>	 <b>152</b>
6.1. Introduction	153
6.2. Experimental Data for Chapter 2	154
6.3. Experimental Data for Chapter 3	188
6.4. Experimental Data for Chapter 4	221
6.5. Experimental Data for Chapter 5	238
 <b>Appendix A. Compound List</b>	 <b>273</b>
<b>Appendix B. Crystallographic Data</b>	<b>281</b>
<b>Appendix C. <sup>1</sup>H NMR Spectra of Selected Compounds</b>	<b>303</b>
<b>References</b>	<b>310</b>

## Abbreviations

Ac	Acetyl
AIBN	2,2'-Azobisisobutyronitrile
APCI	Atmospheric Pressure Chemical Ionisation
Bn	Benzyl
<i>n</i> -Bu	<i>n</i> -Butyl
<i>t</i> -Bu	<i>t</i> -Butyl
Bz	Benzoyl
Cbz	Benzyloxycarbonyl
CI	Chemical Ionisation
COSY	Correlation spectroscopy
<i>m</i> -CPBA	<i>m</i> -Chloroperoxybenzoic acid
DABCO	1,4-Diazabicyclo[2.2.2.]octane
de	Diastereomeric excess
DMAP	4-Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DMP	3,5-Dimethylpyrazole
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i> )-pyrimidinone
DMSO	Dimethylsulfoxide
ee	Enantiomeric excess
EBTHI	Ethylenebis(4,5,6,7-tetrahydro-1-indenyl)
EI	Electron impact
Equiv.	Equivalents
G.L.C.	Gas Liquid Chromatography
IBX	1-Hydroxy-1,2-benziodoxol-3(1 <i>H</i> )-one 1-oxide (2-iodoxybenzoic acid)
IR	Infra Red
LDA	Lithium diisopropylamine
Me	Methyl
NMO	<i>N</i> -Methylmorpholine- <i>N</i> -oxide
NMP	1-Methyl-2-pyrrolidinone

NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Enhancement Spectroscopy
NBS	<i>N</i> -Bromosuccinimide
Nu	Nucleophile
Ph	Phenyl
PDC	Pyridinium dichromate
<i>i</i> -Pr	Isopropyl
Piv	Pivaloyl
SES	(Trimethylsilyl)ethanesulfonyl
TBDMS	<i>tert</i> -Butyldimethylsilyl
TBSOTf	<i>tert</i> -Butyldimethylsilyl trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran-2-yl
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl

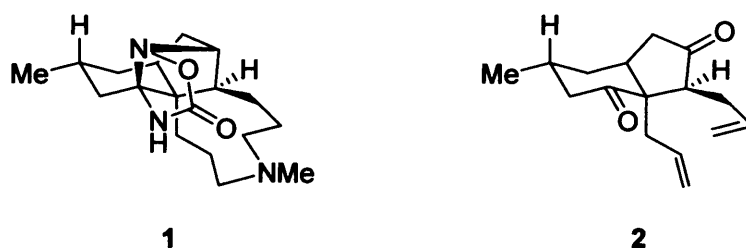


# **Chapter 1**

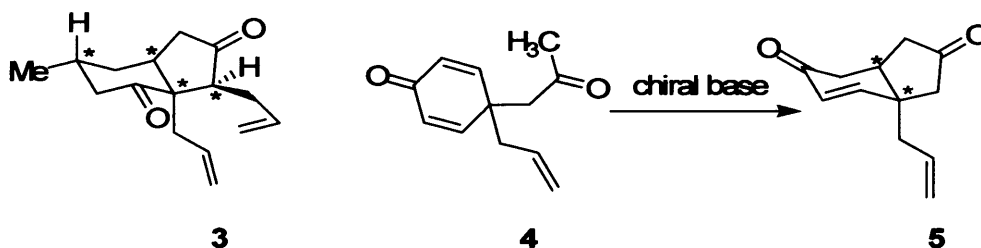
## **Introduction**

### 1.1. Background to the project

The initial inspiration for the chosen methodology is the isolation in 2001 of lycoposerramine A **1**.<sup>1</sup> This complex natural product, isolated from a plant which has produced natural products showing potential for the treatment of Alzheimer's disease, has a number of unique structural features. From the perspective of a synthetic challenge however, it is the heavily functionalised carbobicyclic core **2** which would be a key intermediate.



The diketone **2** has four stereogenic centres, indicated with asterisks on structure **3**, including one quaternary (shown in red) which are generally considered the most difficult to prepare with stereocontrol.<sup>2</sup> In considering approaches to this molecule, a desymmetrisation strategy could be used,<sup>3</sup> exemplified by the conversion of compound **4** into compound **5** to prepare this core ring system. This approach has the distinct advantage of allowing the introduction of two of the stereogenic centres, including the quaternary, in a single step at an early point in the synthesis. Compound **5** is highly functionalised, and in particular would be suitable for elaboration into compound **2** and thence to compound **1**. The ideal approach would feature use of a chiral base to induce the required asymmetry.

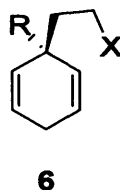


To date there have been no reported approaches to compound **1**, and a structure of this complexity is challenging. Therefore, a large number of model studies will need

to be undertaken in order to demonstrate that the proposed approach is viable. These studies will allow the preparation of a number of compounds related to **5**, all of which will feature the key quaternary stereogenic centre and will be of use as synthetic intermediates in a number of biological areas. Since these compounds are difficult to prepare by more traditional synthetic methods, the development of this methodology will constitute a significant advance, and will eventually allow such a synthesis to become feasible.

In such an undertaking, it is important that the initial approach be relatively straightforward. It is for this reason that the project has moved slightly away from compound **5** and generalised the project somewhat as described in the following section.

The general feature of the conversion of compound **4** into compound **5** is the cyclisation of a suitable precursor such as **6** with simultaneous desymmetrisation.

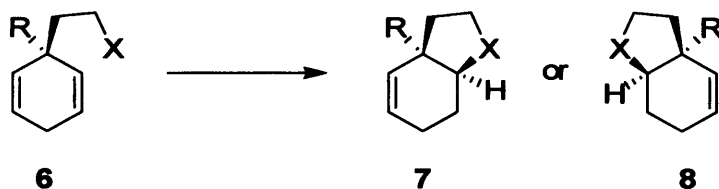


This molecule is achiral. It has an internal mirror plane, so its two double bonds are enantiotopic. There are a large range of possible reactions which can be used to discriminate between its two double bonds. These are shown in the following sections.

## **1.2. Differentiation approaches that occur during a cyclisation step**

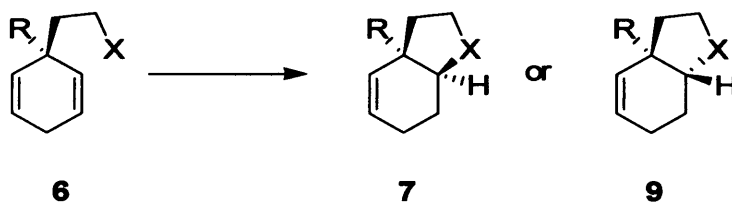
(a) Intramolecular cyclisation of a substrate such as **6** will result in saturation of one of the two double bonds with simultaneous formation of a C-C bond and generation of at least two new highly crowded vicinal stereogenic centres. One of the new stereogenic centres is a quaternary stereogenic centre bearing only carbon substituents which is formed in a single step and without a reaction at that centre. This is generally considered the most difficult type of stereogenic centre to prepare

with stereocontrol. These stereogenic centres make the top and the bottom faces of the molecule different so the cyclisation will result in the formation of enantiomers **7** or **8** depending on which double bond is being attacked (**Scheme 1**).



**Scheme 1**

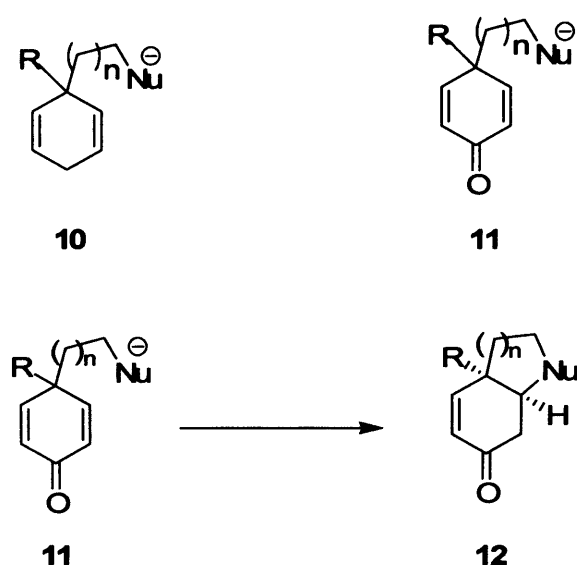
Also the cyclisation of substrate **6** can give rise to diastereoisomers **7** and **9** depending on which face of the double bond is attacked, although formation of rings smaller than seven-membered is likely to favour the *cis*-diastereoisomer **7**.



**Scheme 2**

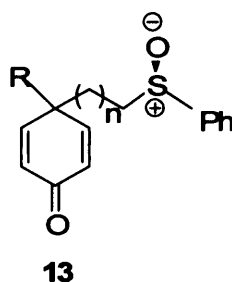
The proposed cyclisation processes should be useful for the construction of complex carbocyclic ring systems such as those found in lycoposerramine A **1**. Also these ring systems can be converted into an array of useful polysubstituted cyclohexanes.<sup>4</sup> Moreover, the second double bond could be functionalised by epoxidation or cyclopropanation or it could even be cleaved by ozonolysis to afford acyclic intermediates rich in adjacent stereogenic centres which can be further elaborated.

There are a wide range of possible substrates for such a reaction, these differing not only in the type and the length of the tethered side chain (reaction partner) but also in the method that can be used for inducing asymmetry. Compound **10** is one such substrate which has a tethered nucleophile. Intramolecular cyclisation of substrate **10** would require an electrophilic double bond such as that in enone **11** shown below to undergo Michael addition to give bicycle **12** (**Scheme 3**).

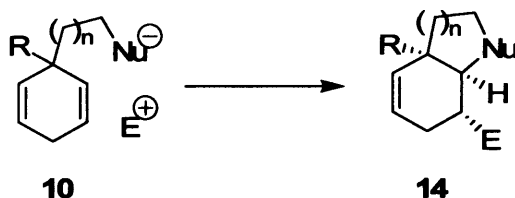


**Scheme 3**

The stereocontrol could be exerted by an external influence such as a chiral base. This approach is ideal, as it could be developed into a catalytic method to afford large amount of optically active products without the need to remove any chiral units. However, it suffers from a distinct practical disadvantage that is the product would be produced as an unequal mixture of enantiomers, which would not be straightforward to assess. Furthermore, a considerable amount of experimentation would be required to determine the optimal chiral reagent and conditions. Alternatively, by introduction of chirality onto the chain *via* a pre-existing stereogenic centre covalently bound to the cyclohexadiene ring, the differentiation of the two double bonds in 1,4-cyclohexadiene would be categorised as a diastereoselective reaction. This approach has one major disadvantage – the chiral influence is retained in the product, and would require additional steps to remove. On the other hand this can be advantageous since it would be producing diastereomeric products which would be easy to assay. There are a broad range of potential substrates with a variety of stereochemical directing groups. Toward this application, sulfoxide side chains have been chosen as the chiral influence (*e.g.* in general structure 13). This group could be readily removed<sup>5</sup> to generate the enantiomerically-enriched products. A further disadvantage of chiral auxiliaries is that a stoichiometric amount of the chiral group is required.

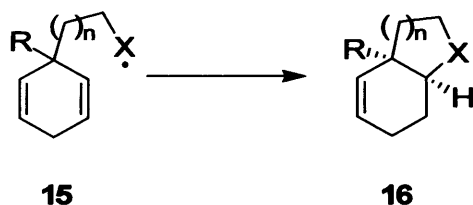


(b) As an alternative, the cyclisation could be triggered by an electrophile, such as iodine or (for example) a phenylselenenyl halide. In either case, the possibility of enantioselective reactions exist by use of chiral modifiers for the iodocyclisation<sup>6</sup> or chiral selenium electrophiles<sup>7</sup> in that particular case. This is shown in the general case by the conversion of **10** into **14** (Scheme 4).



**Scheme 4**

(c) Finally, the cyclisation of a free-radical onto a cyclohexadiene ring should be considered (**15** → **16**) with the aim of elucidating the conformational bias in such systems. There are a broad range of radical precursors that can be used, among them alkyl halides and xanthate side chains that can be regioselectively and diastereoselectively cyclised onto one of the two alkene double bonds under the influence of a stereochemical directing group (Scheme 5).



**Scheme 5**

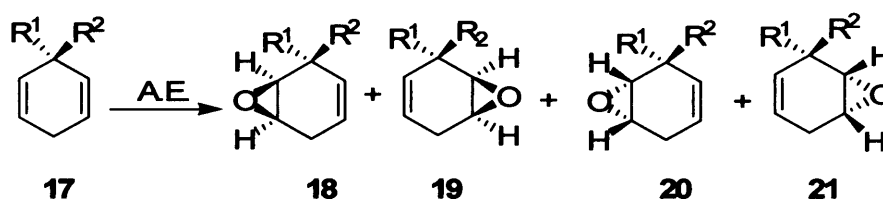
In all of these examples, the length of the chain (and hence the size of ring formed) can be varied. Furthermore, a range of heteroatoms can be introduced into this chain.

The atom type of the nucleophile can be varied (C, N, O) in the first two instances, along with the electrophile (Br, I, Se) in the second approach. This means that the general approach investigated will have a broad range of applicability in organic synthesis.

### 1.3. Enantioselection approaches before any cyclisation reaction

It is possible to desymmetrise a diene before any cyclisation reaction. This would most likely be done using asymmetric oxidation chemistry.

Epoxidation of compound **17** could give rise to the formation of four stereoisomers **18**, **19**, **20** and **21** depending of the effect of the substituents  $R^1$  and  $R^2$  in directing the epoxidation to the top or the bottom face of each double bond as shown in **Scheme 6**.



**Scheme 6**

Compounds **18** and **20** are diastereoisomers, as are compounds **19** and **21**. Compounds **18** and **19** are enantiomers as are compounds **20** and **21**. The nature of  $R^1$  and  $R^2$  will direct the epoxidation to be *syn* or *anti* to one of these substituents resulting in formation of one of the two diastereoisomers in higher ratio than the other.

The use of a chiral catalyst (*e.g.* Jacobsen-Katsuki Mn(salen) complex) could then direct the epoxidation to be enantioselective, *i.e.* which double bond will be attacked. This particular reaction is particularly good for cyclic *cis* alkenes, so that good enantioselectivity should be observed.

#### 1.4. Previous desymmetrisation reactions of cyclohexadienes

According to the literature there are two fundamental ways to discriminate between the two double bonds in 1,4-cyclohexadienes depending on their nature.

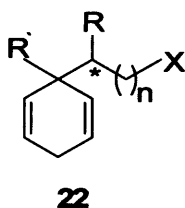
1. Approaches that can desymmetrise chiral cyclohexadienes (Diastereotopic group selections). Here, the chirality present within the molecule directs attack to one or other of the double bonds.
2. Approaches that can desymmetrise achiral cyclohexadienes (Enantiotopic group selections). In this case the selection will be carried out by using an external chiral influence.

##### 1.4.1. Diastereotopic group selection

In this case the differentiation will be performed by a pre-existing stereogenic centre somewhere in the substrate. These approaches can be subdivided according to the position of the stereogenic centre in the substrate.

##### 1.4.1.1. Desymmetrisation approaches of cyclohexadienes having the stereogenic centre within the tether

These processes take place either through cycloaddition reactions into a substrate having the general structure as **22** or through conjugate addition reactions using oxygen or nitrogen nucleophiles or through radical cyclisation processes.

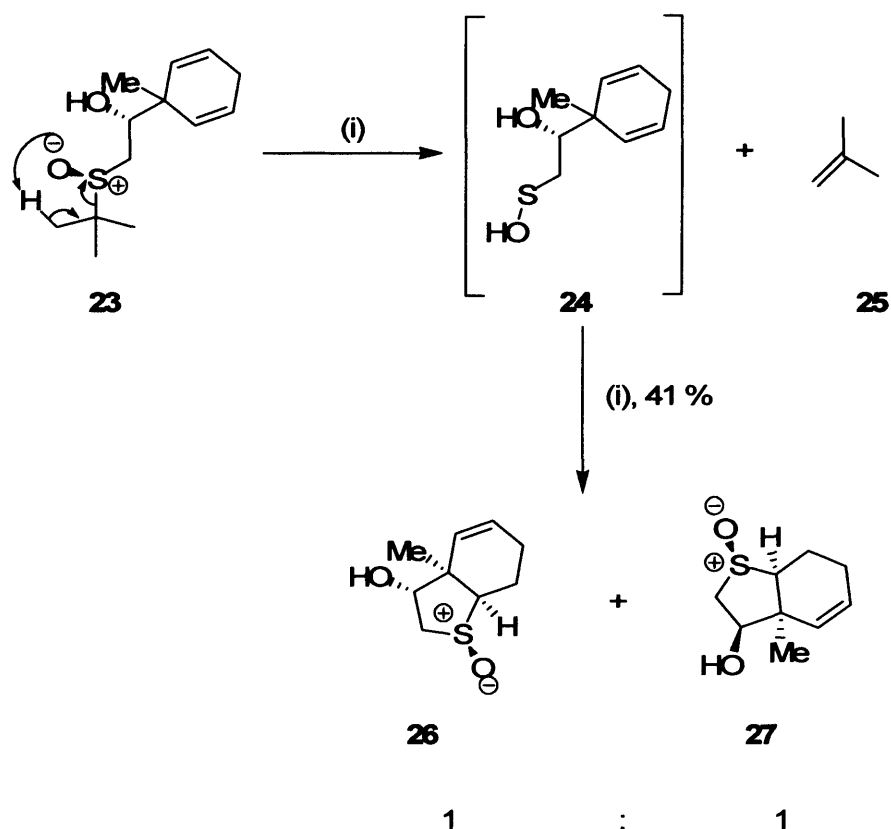


##### 1.4.1.1.1. Cycloaddition reactions

Grainger and co-workers<sup>8</sup> demonstrated that the ratio of diastereoselectivity in *cis*-fused perhydrobenzothiophene *S*-oxides formed by the intramolecular addition of a sulfenic acid to 1,4-cyclohexadiene can be controlled by the nature of the protecting group on a chiral alcohol **23** in the tether. Thermolysis of the readily synthesised alcohol **23** was accompanied by elimination of isobutene **25** and formation of intermediate sulfenic acid **24** which underwent an unselective

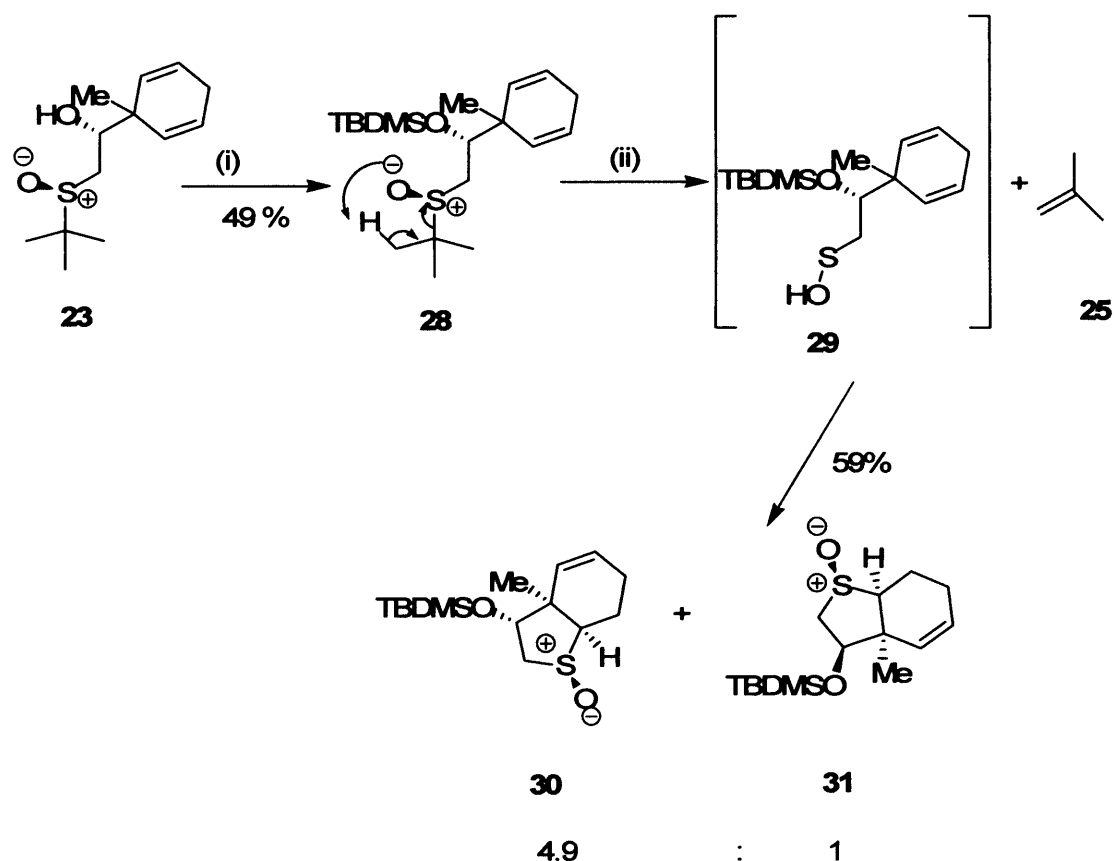


intramolecular cycloaddition to provide a mixture of two perhydrobenzothiophene *S*-oxides **26** and **27** in a 1:1 ratio as shown in **Scheme 7**.



**Scheme 7** *Reagents and conditions:* (i) Xylene, reflux.

The diastereoselectivity was improved by protecting the starting alcohol with different groups of varying steric and electronic properties. The highest ratio (major:minor 4.9:1) was obtained when the OH group was protected as a TBDMS ether as shown in compounds **30** and **31** respectively (**Scheme 8**).

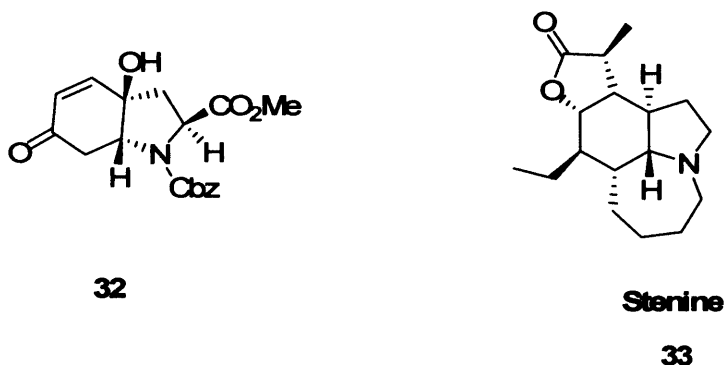


**Scheme 8** *Reagents and conditions:* (i) TBDMSCl, imidazole, DMF; (ii) Xylene, reflux.

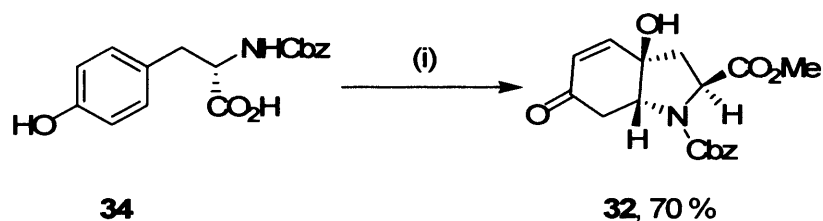
The obtained selectivity was attributed to a thermodynamic rather than kinetic preference, since resubjecting single isomers of isolated products to the same reaction conditions gave identical mixtures of diastereoisomers.<sup>8</sup>

#### 1.4.1.1.2. Conjugate addition reactions

Wipf and his group reported a concise approach toward the preparation of the key bicycle compound **32**. Intermediate **32** has general use in pyrrolidine alkaloid synthesis and it was applied in the asymmetric synthesis of alkaloid (-)-stenine **33** which has many medicinal applications.<sup>9</sup>

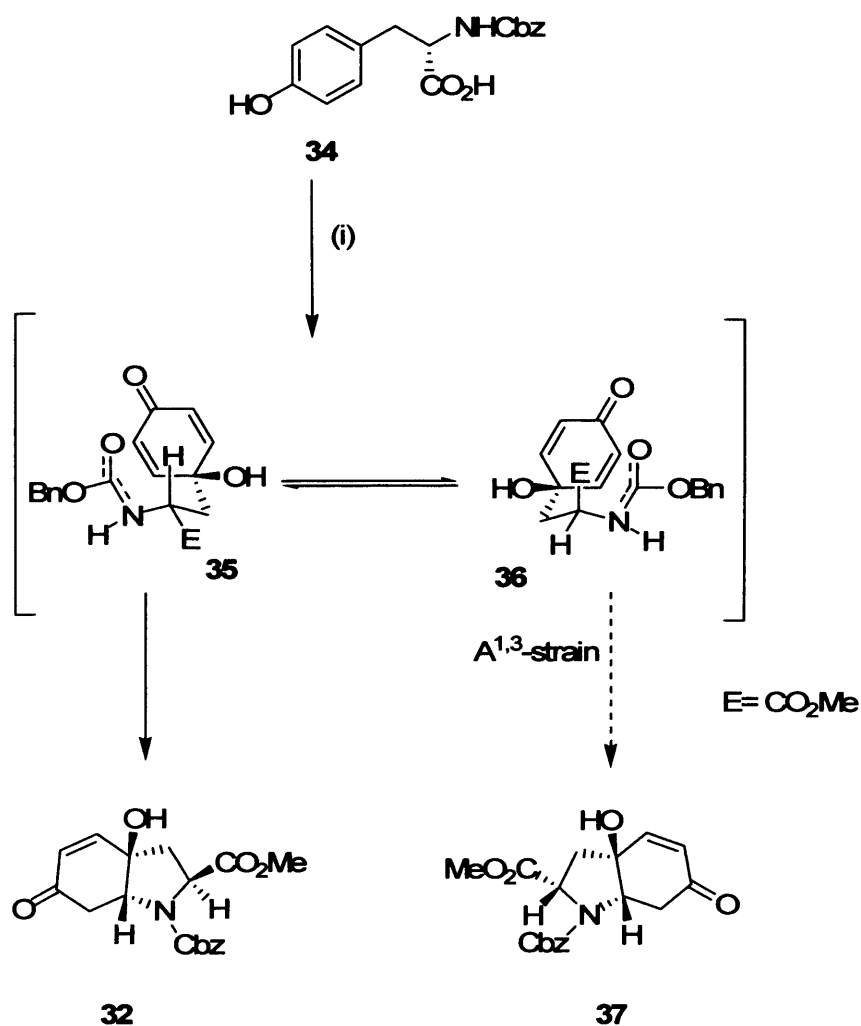


Synthesis of the bicycle **32** proceeded in a single step from Cbz-tyrosine **34**, using sodium hydrogen bicarbonate and iodobenzene diacetate. The key intermediate **32** was obtained in enantio- and diastereomerically pure form as shown in **Scheme 9**.



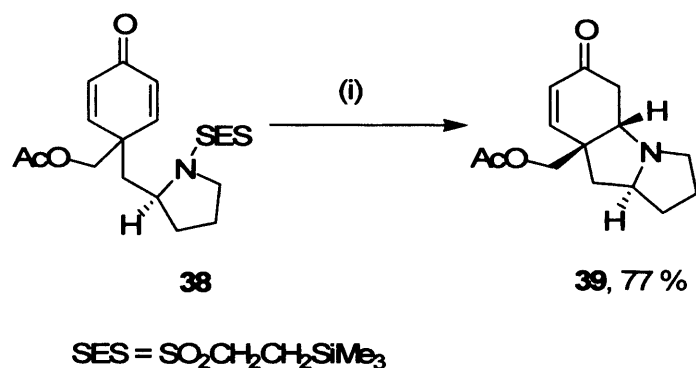
**Scheme 9** *Reagents and conditions:* (i) PhI(OAc)<sub>2</sub>, NaHCO<sub>3</sub>, MeOH, 23 °C, 23 h.

The high selectivity obtained was attributed to the conformational rigidity of the substrate which resulted in destabilising steric interactions in conformer **36**, especially A<sup>1,3</sup>-strain between the carbamate oxygen and the methyl ester (*E*) substituent. Moreover, face-to-face interaction of the *trans*- carbamate and enone  $\pi$ -systems in the transition state for the cyclisation positions the ester function in conformer **36** underneath the dienone in a sterically crowded environment. Traces of the unfavoured isomer **37** were obtained under forcing conditions, *e.g.* at temperatures higher than 100 °C in DMSO (**Scheme 10**).



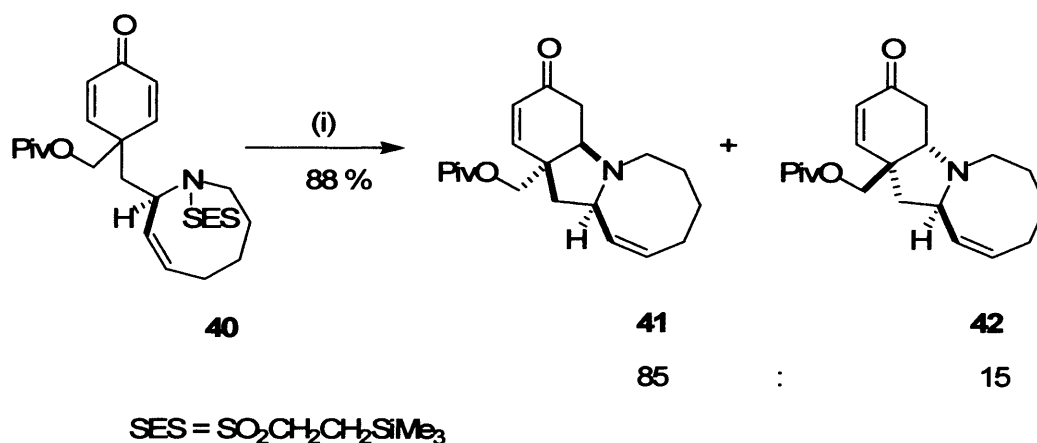
**Scheme 10** Reagents and conditions: (i)  $\text{PhI}(\text{OAc})_2$ ,  $\text{NaHCO}_3$ ,  $\text{MeOH}$ , 21 – 40 °C.

Hart and his group<sup>10</sup> showed that nucleophilic amines can be used to desymmetrise cyclohexadienone derivatives with high diastereomeric excess. Their approach was based on desilylation of amino cyclohexadienone **38** using caesium fluoride in *N,N*-dimethylformamide at 90 °C. The deprotection was accompanied by formation of tricyclic perhydropyrrolo[1,2-*a*]indole **39** as a sole stereoisomer in 77 % yield as shown in **Scheme 11**.



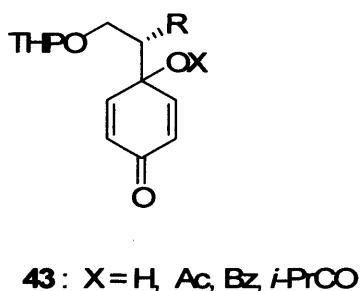
**Scheme 11** Reagents and conditions: (i) CsF, DMF, 90 °C, 15 h.

Hart and co-workers then reported that amino cyclohexadienone **40** underwent a diastereoselective intramolecular conjugate addition to afford enones **41** and **42** in an approximately 85:15 ratio respectively in 88 % crude yield under the same reaction conditions (**Scheme 12**).<sup>11</sup>

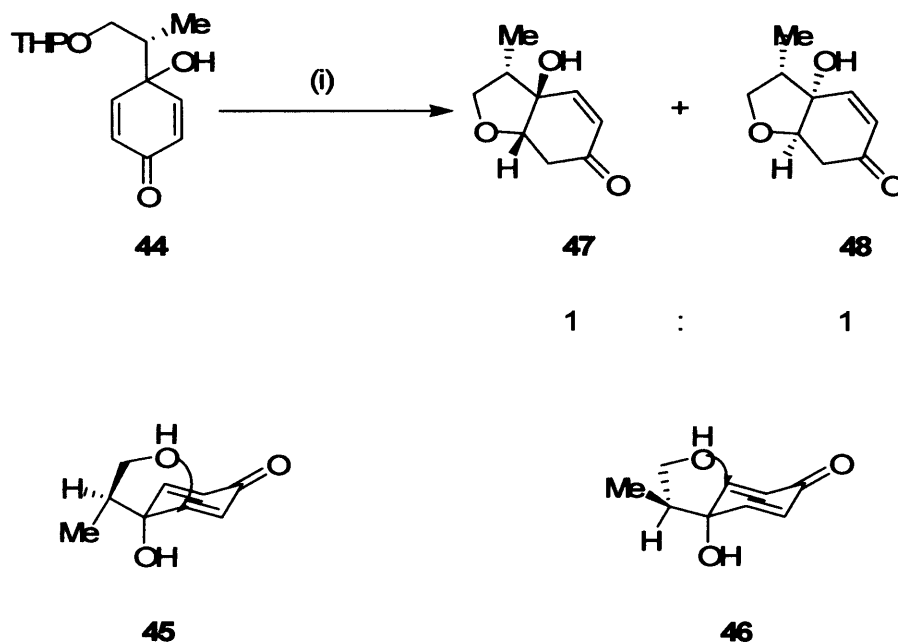


**Scheme 12** Reagents and conditions: (i) CsF, DMF, 90 °C, 15 h.

Fujioka and co-workers demonstrated that *O*-nucleophiles can be used to desymmetrise the two double bonds of quinol derivative **43** under the influence of a pre-existing stereogenic centre in the tether.<sup>12</sup>

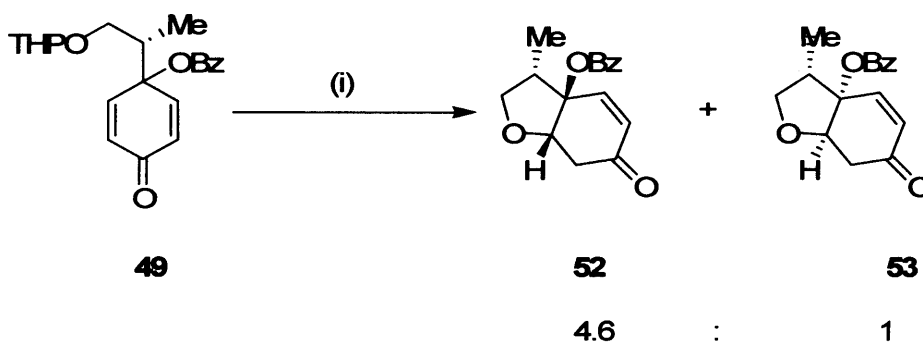


Deprotection of compound **44** liberated the *O*-nucleophile and was accompanied by diastereotopic group selective-intramolecular 1,4-conjugate addition which resulted in formation of the cyclised products **47** and **48**. However, there was no diastereoselectivity (**47**:**48** = 1:1). The lack of selectivity was attributed to the fact that there was no preferred conformation between the two transition states **45** and **46** proposed for the cyclisation process (**Scheme 13**).



**Scheme 13** *Reagents and conditions:* (i) 90 % aqueous acetic acid, 50 °C.

However, protection of the hydroxyl group in **44** as an acyl derivative promoted the diastereoselectivity. The benzoyl group was the best choice among the acyl groups studied. Therefore acid treatment of **49** afforded the cyclised products **52** and **53** (major: minor ratio = 4.6:1) as shown in **Scheme 14**.



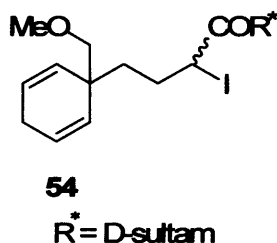
**Scheme 14** *Reagents and conditions:* (i) 90 % aqueous acetic acid, 50 °C.

The transition state models suggested that the benzoylated compound would exist as conformers **50** and **51**, where the bulky ester group occupies the equatorial position. Therefore, conformer **50** is favoured over conformer **51** because of the repulsion between the ring and the substituent of the side-chain in conformer **51** resulting in isomer **52** being formed in preference to isomer **53**.



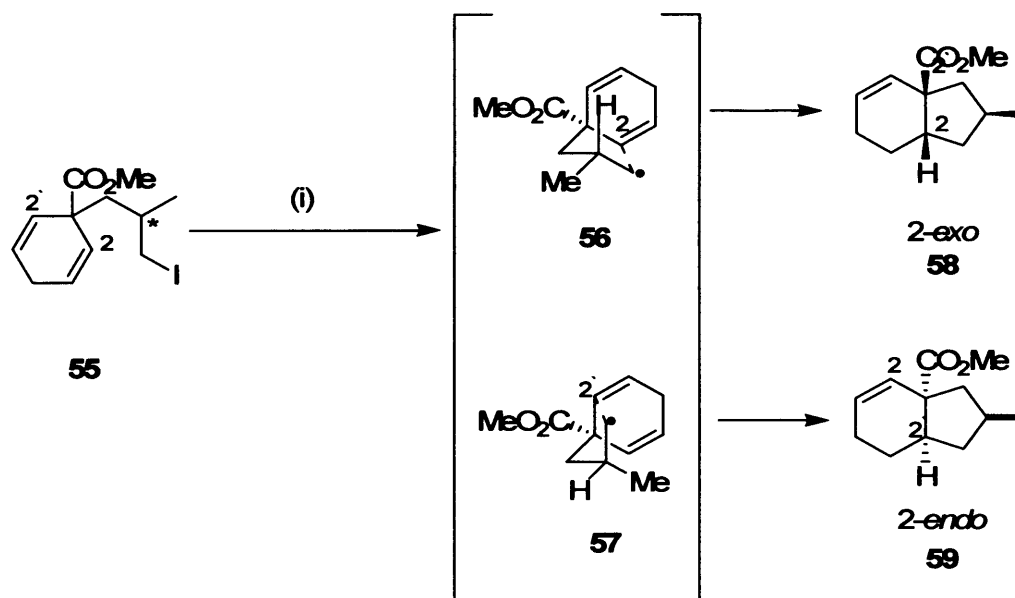
#### 1.4.1.1.3. Free-radical reactions

It has been shown that the stereoselective radical reactions of a diene can operate under substrate control. For example Curran and co-workers previously reported free radical cyclisation under the influence of a remote stereogenic centre using substrate **54** which resulted in modest stereoselectivity as will be discussed later (page 18).



Then Curran succeeded to improve the selectivity by using a simpler substrate **55**.<sup>13</sup> Cyclisation of iodide **55** with tributyltin hydride afforded an inseparable mixture of 2-*exo* and 2-*endo* products **58** and **59** with temperature-dependent selectivities. Conducting the reaction at 80 °C in the presence of 5 mol% AIBN as the initiator provided the *exo:endo* ratio of 15:1 in 82 % yield while conducting the reaction at -78 °C in the presence of triethylborane improved the ratio to 31:1 (66 % yield). The obtained selectivity was attributed to the stability of the chair-like radical transition state **56** with the “equatorial” methyl group that leads to the 2-*exo* product **58** compared to the chair-like radical transition state **57** that leads to the 2-*endo*

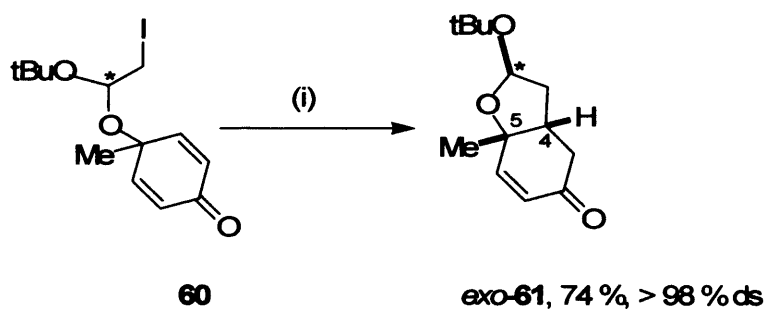
product **59** because addition of the radical to the diastereotopic alkene places the methyl group in an “axial” orientation. This result was in line with their prediction using the models which indicated that transition state **56** is of lower energy therefore it should be favoured (**Scheme 15**).



**Scheme 15** Reagents and conditions: (i) Bu<sub>3</sub>SnH, AIBN, 80 °C; or Bu<sub>3</sub>SnH, Et<sub>3</sub>B, -78 °C.

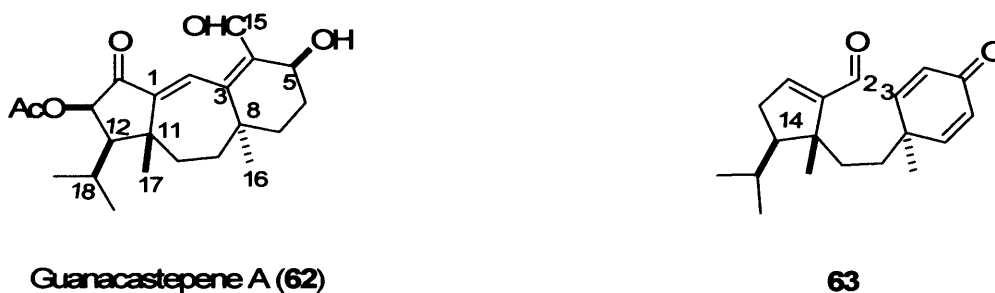
Renaud and co-workers<sup>14</sup> demonstrated their efforts to define the scope and limitations of 5-*exo* radical cyclisation of different haloacetals where the acetal centre is the unique stereogenic element. The initial results indicated that the acetal centre could control the stereochemical outcome of the cyclisation process resulting in the formation of tetrahydrofuran derivatives with high diastereoselectivity in favour of the *exo* isomer where the stereochemistry at C(4) and C(5) is fully controlled. Therefore, tributyltin hydride and triethylborane/oxygen as initiator mediated radical cyclisation of iodide **60** to afford bicycle **61** as a single diastereoisomer in good yield (**Scheme 16**).



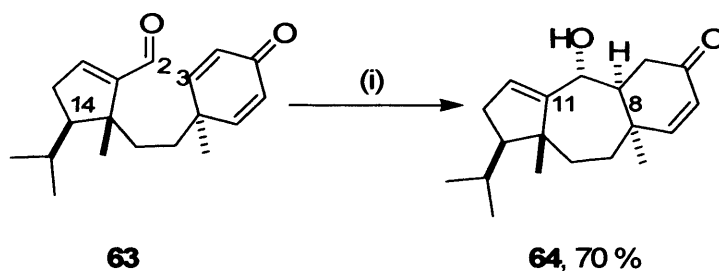


**Scheme 16** Reagents and conditions: (i)  $\text{Bu}_3\text{SnH}$ ,  $\text{Et}_3\text{B}/\text{O}_2$ ,  $-78^\circ\text{C}$ .

Lee and co-workers<sup>15</sup> described the synthesis of the 5-7-6 core of the antibacterial agent guanacastepene A **62**. They designed the precursor aldehyde **63** that could differentiate between the diastereotopic  $\text{C}_3\text{-C}_4$  and  $\text{C}_6\text{-C}_7$  double bonds during the cyclisation reaction by forming the  $\text{C}_2\text{-C}_3$  bond to effect the desired seven-membered ring closure.



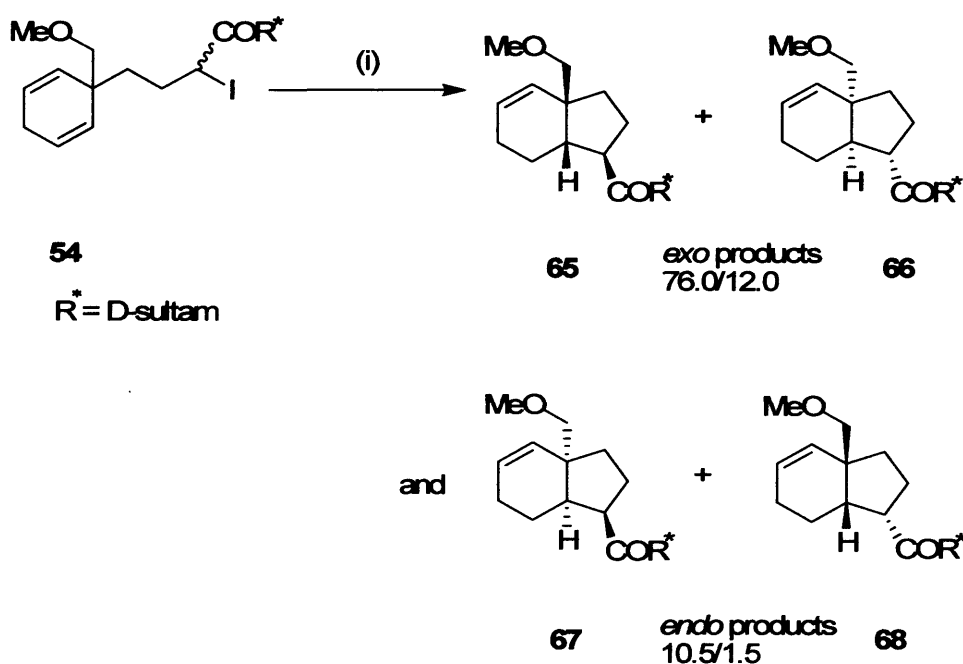
The proposed postulate was based on the fact that the sterically more favourable *trans* relationship between the two ring-junction quaternary angular methyl groups  $\text{C}_{16}$  and  $\text{C}_{17}$  in the natural guanacastanes is the result of a thermodynamically driven process. This prediction was borne out by the experimental results since the ketyl radical cyclisation of aldehyde **63** using  $\text{SmI}_2$  afforded a single isomer of the tricyclic core **64** of guanacastane in 70 % yield (**Scheme 17**).



**Scheme 17** Reagents and conditions: (i)  $\text{SmI}_2$ , *t*-BuOH, THF,  $25^\circ\text{C}$ .

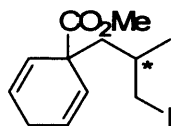
#### 1.4.1.2. Desymmetrisation approaches of cyclohexadienes having the stereogenic centre outside the tether

In this case the asymmetric induction is exerted by a stereogenic centre located outside the tether being used to accomplish the discrimination. There are only three examples in the literature of such a process. The first example was reported by Curran and co-workers using reductive free radical cyclisation process.<sup>16</sup> They demonstrated the cyclisation of iodosultam **54** under the influence of the remote attached chiral Oppolzer's camphorsultam. This cyclisation provided a mixture of four cyclised products, two *exo* (**65** and **66** major) and two *endo* (**67** and **68**) in 76/12/10.5/1.5 ratio respectively. The combined *exo:endo* ratio is 88:12 which was somewhat lower than the ratio they anticipated (92:8) based on their stereochemical model of face selectivity (**Scheme 18**).



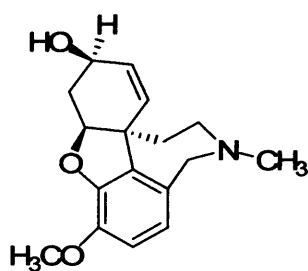
**Scheme 18** Reagents and conditions: (i) Bu<sub>3</sub>SnH, AIBN, 80°C.

Then Curran succeeded to improve the selectivity by using a simpler substrate **55** as discussed above (page 16).



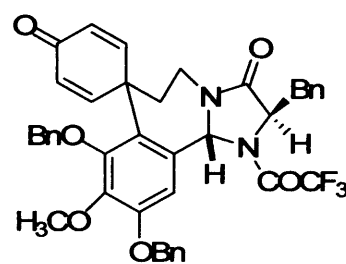
**55**

The second example was demonstrated by Node and co-workers, who reported the total asymmetric synthesis of (-)-galanthamine **69**,<sup>17</sup> an alkaloid that showed potential for treatment of Alzheimer's disease.<sup>18</sup> Substrate **70** was designed so that deprotection would occur to generate the nucleophilic oxygen atom that would preferentially attack one of the two electrophilic diastereotopic double bonds. The asymmetric induction was exerted by the remote stereogenic centre in the imidazolidinone ring, and was enforced by the restricted conformation of the seven-membered ring.



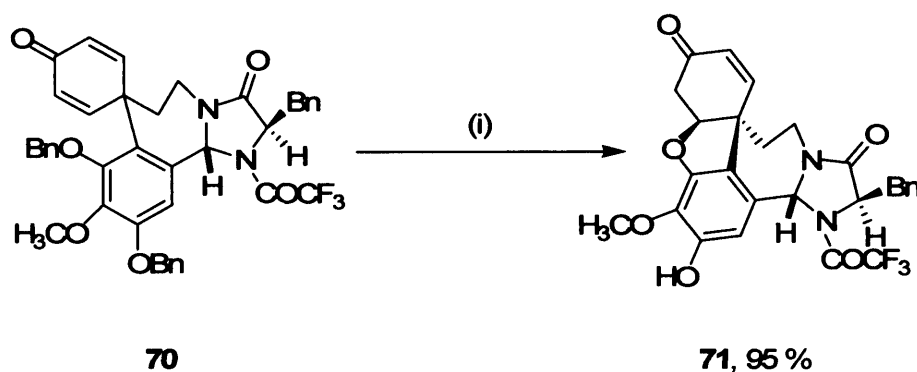
(-)-Galanthamine

**69**



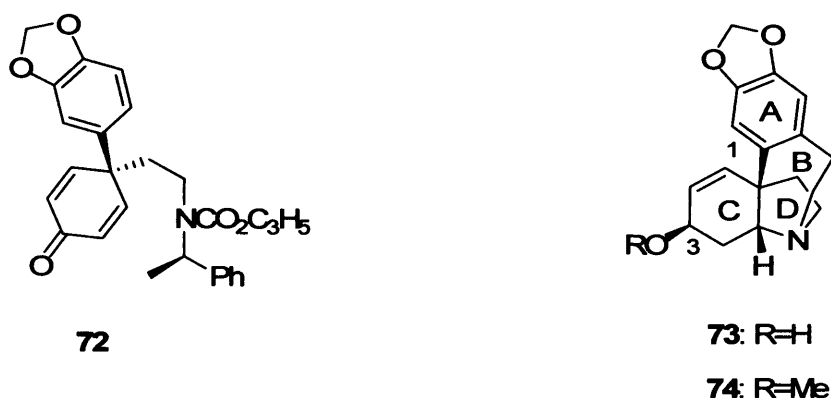
**70**

Thus, debenzoylation of **70** with boron trichloride was accompanied by Michael addition and afforded the cyclic ether **71** as a single diastereoisomer in 95 % yield (Scheme 19).

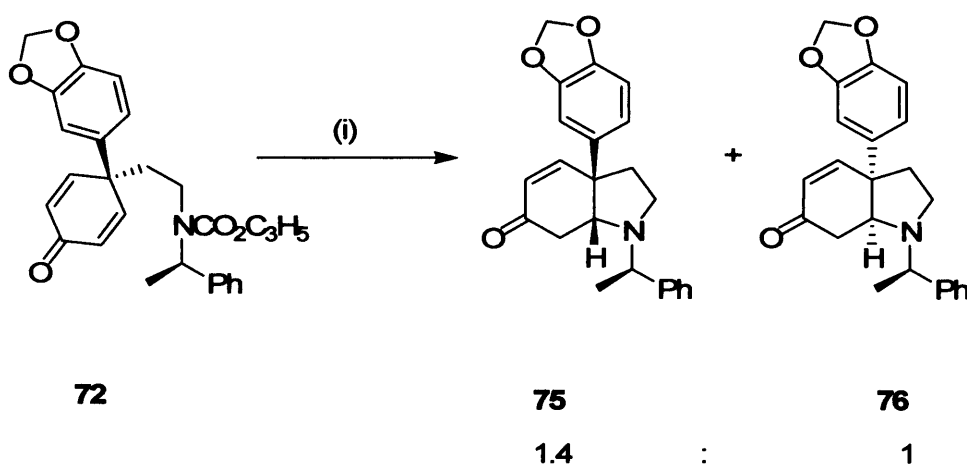


**Scheme 19** Reagents and conditions: (i)  $\text{BCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^\circ\text{C}$ , 2 days.

The third example found in the literature using the stereogenic outside the tether to perform the asymmetric induction was described by Martin and Campbell,<sup>19</sup> who applied a strategy based on desymmetrisation of cyclohexadienone **72** to effect asymmetric synthesis of both crinine **73** and buphanisine **74**.



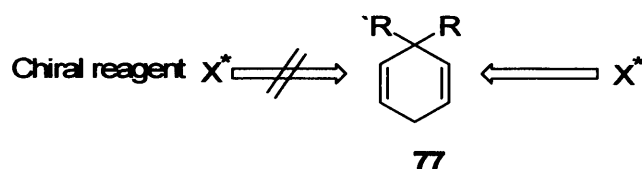
Palladium(0)-catalysed cleavage of the *N*-(allyloxy)carbonyl protecting group in compound **72** generated the nucleophilic intermediate secondary amino cyclohexadienone which underwent spontaneous Michael addition to the enone moiety. The asymmetric induction was exerted by the stereogenic carbon on the *N*-alkyl protecting group and it resulted in the formation of an inseparable mixture of diastereomeric hydroindolenones **75** and **76** in very low diastereoselectivity (1.4:1.0 by  $^1\text{H}$  NMR spectroscopy) (**Scheme 20**).



**Scheme 20** Reagents and conditions: (i)  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Ph}_3\text{P}$ , 2-ethylhexanoic acid.

#### 1.4.2. Enantiotopic group selection

In this case the desymmetrisation of an achiral 1,4-cyclohexadiene will be under the influence of an external chiral reagent such as AD-mix formulations, chiral dioxiranes or Brown's dilongifoleneborane and diisopinocampheylboranes. These processes take place either through asymmetric dihydroxylation, aminohydroxylation, epoxidation and hydroboration reactions of a substrate having the general structure **77** (Figure 1).

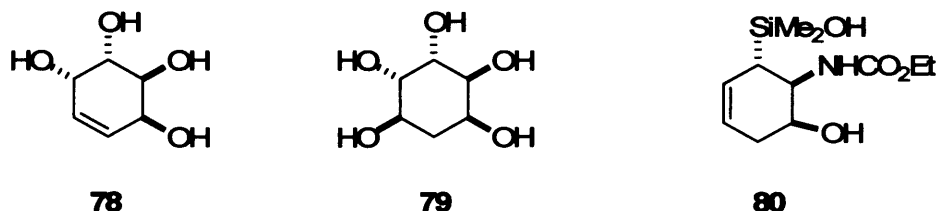


**Figure 1** Enantiotopic group differentiation in 1,4-cyclohexadiene

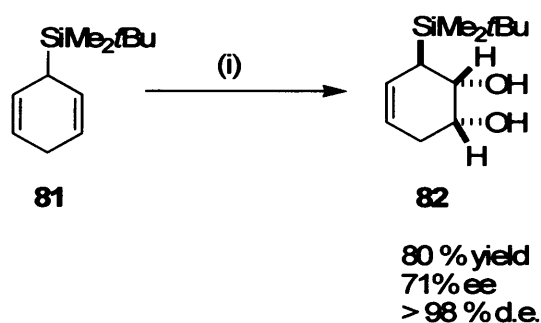
Alternatively, transition metal mediated processes including palladium mediated processes (*e.g.* intramolecular Heck reaction), or zirconium mediated process or copper mediated processes (*e.g.*  $\text{Cu}(\text{I})$ -catalysed intramolecular cyclopropanation) can be used to desymmetrise 1,4-cyclohexadienes. These processes were accompanied by generation of chiral quaternary centres.

Landais and his group demonstrated a general method to desymmetrise readily available silylcyclohexa-2,5-dienes using Sharpless asymmetric dihydroxylation and aminohydroxylation to deliver cyclohexadiene derivatives having four or five stereogenic centres in a stereocontrolled manner.<sup>20</sup> Among the products prepared

using this method are cyclitols **78**, and **79** which have inhibiting activities toward glycosidases and amino-cyclitols such as **80** which was used as precursor for the synthesis of fortamine, the aglycon moiety of the antibiotic *fortimicins*.



Landais and his group chose to use the silylated substrates in the expectation that the bulky silyl group would control the diastereoselectivity. Therefore it would direct the dihydroxylation to be in an *anti* fashion. Then the chiral osmium reagent would be able to differentiate the two enantiotopic double bonds. Their postulate turned out to be correct concerning the diastereoselectivity issue where they subjected silylated and non-silylated dienes to Sharpless asymmetric dihydroxylation conditions and they found that the de (%) in case of silylated substrates was not less than 98 % while in case of non silylated substrates the de (%) was in a range from 40 - 88 %. With regard to the enantioselectivity, they used different AD-mix formulations and they found that the best enantioselectivities were obtained with (DHQ)<sub>2</sub>PYR. Subjecting substrate **81** to these conditions afforded diol **82** in > 98 % de, 71 % ee, and in 80 % yield (Scheme 21).



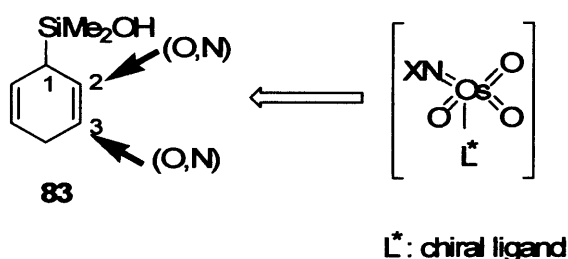
**Scheme 21** Reagents and conditions: (i) K<sub>2</sub>OsO<sub>4</sub>, 2H<sub>2</sub>O, K<sub>3</sub>Fe(CN)<sub>6</sub>, MeSO<sub>2</sub>NH<sub>2</sub>, (DHQ)<sub>2</sub>PYR, *t*-BuOH/H<sub>2</sub>O 1:1, 0 °C.

This moderate enantioselectivity was not surprising for the group because they considered the observations made by Sharpless and co-workers<sup>21</sup> which indicated

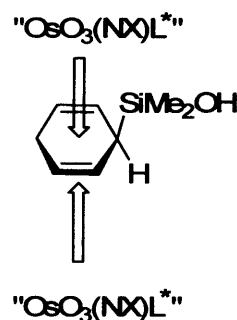
that Z-olefins and cyclic olefins usually give poor results using commercially available AD-mix ((DHQ)<sub>2</sub>PHAL).

The same group also desymmetrised 1-silylcyclohexa-2,5-diene derivatives using an aminohydroxylation reaction.<sup>22</sup> In this case there is a regiochemical issue, since either oxygen or nitrogen can attack at C-2 or C-3 (**Scheme 22**).

**Enantiotopic group differentiation  
Regioselectivity**

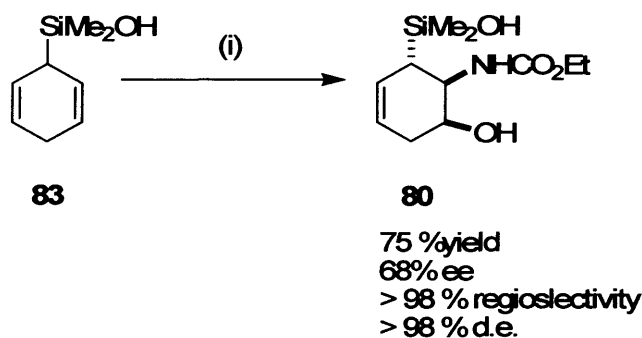


**Diastereofacial differentiation**



**Scheme 22**

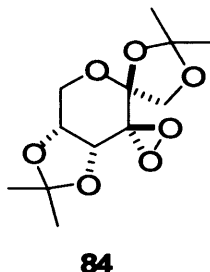
Applying the aminohydroxylation reaction to silanol **83** afforded the amino alcohol **80** with high regio- and diastereoselectivity and with good enantiocontrol (**Scheme 23**).



**Scheme 23** *Reagents and conditions:* (i) K<sub>2</sub>OsO<sub>4</sub>, 2H<sub>2</sub>O, (DHQ)<sub>2</sub>PYR, H<sub>2</sub>NCO<sub>2</sub>Et, NaOH, *t*-BuOCl, *i*-PrOH/H<sub>2</sub>O, r.t.

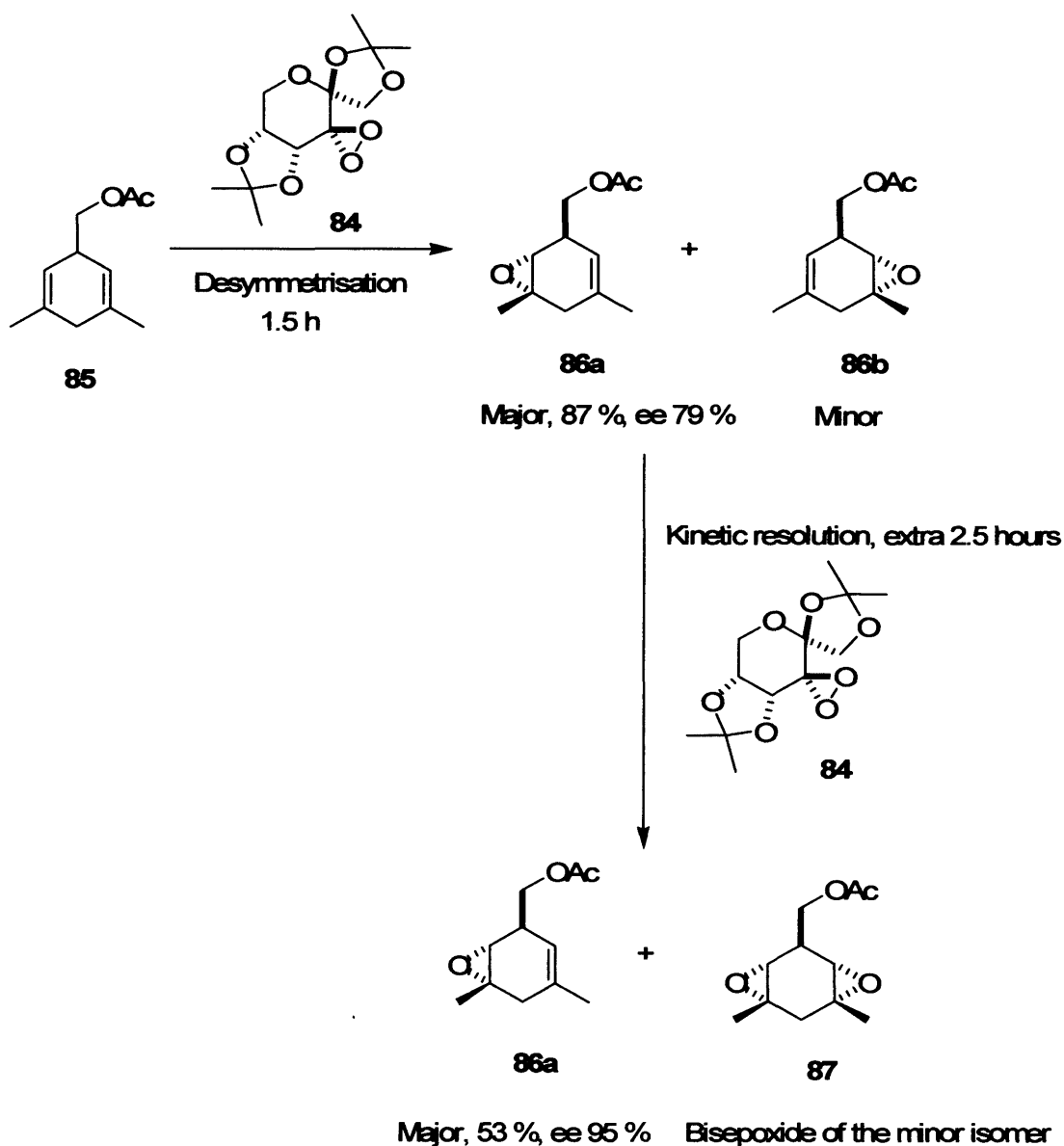
The observed regioselectivity where the carbamate group attacked preferentially at the slightly more hindered C-2 position was attributed to electronic directing effects operating during the differentiation process.

Shi and his group<sup>23</sup> described desymmetrisation of 1,4-cyclohexadiene coupled with a subsequent kinetic resolution processes using chiral dioxirane **84** generated *in situ* from the corresponding fructose-derived ketone and oxone.



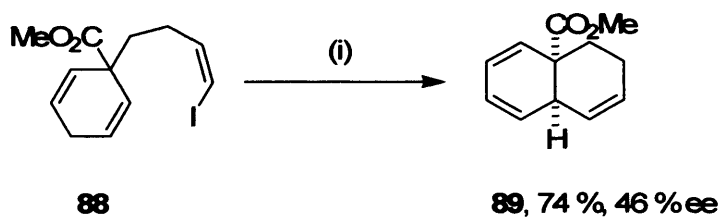
Generally in kinetic resolution processes,<sup>24</sup> the minor enantiomer from the first asymmetric transformation could be preferentially consumed in a second transformation as the reaction proceeds, leading to enhancement of the optical purity of the major enantiomer. For example, desymmetrisation-kinetic resolution processes proceeded efficiently for diene **85** having a prochiral centre proximal to the two enantiotopic double bonds to direct the epoxidation. The initial desymmetrisation resulted in formation of monoepoxide **86a** as the major enantiomer and monoepoxide **86b** as the minor enantiomer where the oxygen preferentially delivered *anti* to the acetate group. The ee of the major monoepoxide was found to be 79 %. This ratio gradually increased with time (79 % to 95 % from 30 to 240 min.). This increase is due to in the second epoxidation, the minor isomer was preferentially epoxidised to the bis-epoxide **87** and consumed faster than the major isomer, resulting in an improvement of the enantioselectivity, but this was accompanied with a decrease in the yield (87 % to 53 % from 30 to 240 min.) (Scheme 24).





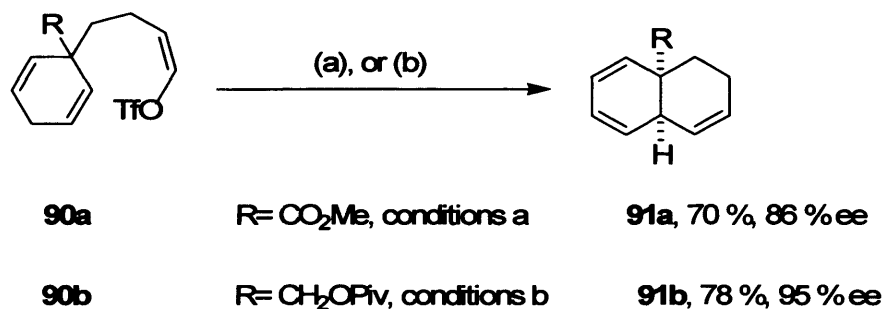
**Scheme 24**

Shibasaki and his group<sup>25</sup> reported the first example of asymmetric C-C bond formation *via* Heck-type reaction using cyclohexadiene **88**, Pd(OAc)<sub>2</sub> and optically active bidentate ligands in the presence of Ag<sub>2</sub>CO<sub>3</sub> and 1-methyl-2-pyrrolidinone (NMP) as solvent. This resulted in desymmetrisation of cyclohexadiene **88** and formation of *cis*-decalin derivative **89** in a stereo- and regiocontrolled manner but in modest enantiocontrol (46 % ee) (**Scheme 25**).



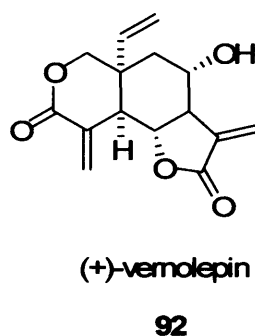
**Scheme 25** Reagents and conditions: (i) Pd(OAc)<sub>2</sub>, (*R*)-BINAP, NMP, Ag<sub>2</sub>CO<sub>3</sub>, 60 °C, 3 h.

Then the same author improved the enantioselectivity by using triflate **90a** and **90b** associated by changing the reaction conditions including the solvents and the additives such as alcohol and acetate anion to have the decalins **91a** and **91b** in up to (70 % yield and 86 % ee) and (78 % yield and 95 % ee) respectively<sup>26</sup> (**Scheme 26**).

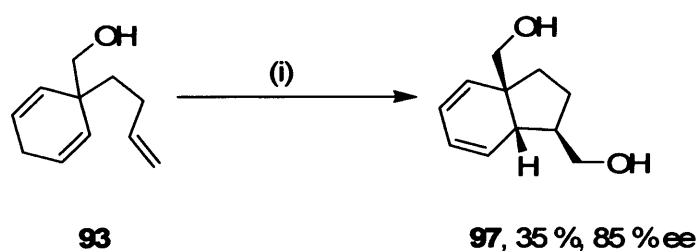


**Scheme 26** Reagents and conditions: (a) Pd(OAc)<sub>2</sub>, (*R*)-BINAP, K<sub>2</sub>CO<sub>3</sub>, KOAc, CH<sub>2</sub>Cl<sub>2</sub>, 60 °C, 41 h; (b) Pd(OAc)<sub>2</sub>, (*R*)-BINAP, K<sub>2</sub>CO<sub>3</sub>, pinacol, CH<sub>2</sub>Cl<sub>2</sub>, 60 °C, 47 h.

Using decalin **91a** this group reported the first asymmetric synthesis of the natural antitumour agent (+)-vernolepin **92** and determined its absolute stereochemistry.

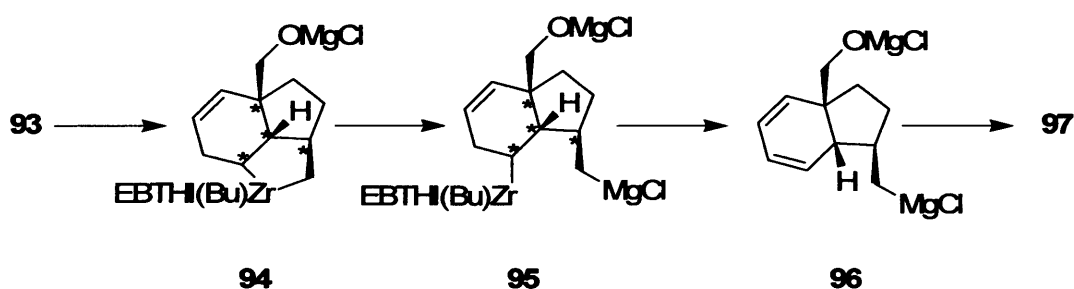


A zirconium mediated enantiotopic group-selective synthesis of hydrindane **97** was demonstrated by Mori and co-workers.<sup>27</sup> When they treated triene **93** with (*S*)-(EBTHI)Zr(BINOL) and butyl magnesium chloride, the enantiotopic group-selective cyclisation proceeded and the new C-C bond was formed preferentially between the exocyclic double bond and one of the two enantiotopic endocyclic double bonds to provide compound **97** as a single diastereoisomer with 85 % ee in 35 % yield (**Scheme 27**).



**Scheme 27** Reagents and conditions: (i) (*S*)-(EBTHI)Zr(BINOL), BuMgCl, THF, reflux 4 h.; (ii) O<sub>2</sub>

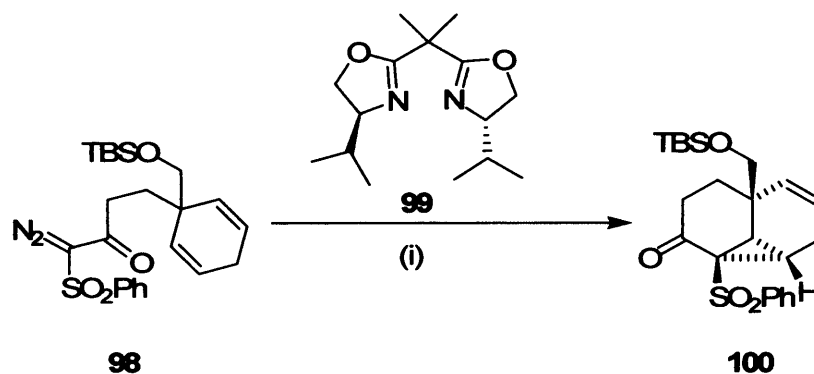
Mori and co-workers proposed that the reaction proceeded *via* the *trans*-fused 5-5-membered zirconacycle **94** which further reacted with butyl Grignard reagent and converted into alkyl-Zr intermediate **95** which then underwent β-hydride elimination to give **96** which upon treating with oxygen afforded the isolated diol **97** (**Scheme 28**).



**Scheme 28** Possible reaction course

Nakada and Honma desymmetrised cyclohexadiene through Cu(I)-mediated intramolecular enantioselective cyclopropanation.<sup>28</sup> Using substrate **98** and the

asymmetric catalyst prepared *in situ* by  $(\text{CuOTf})_2\text{-C}_6\text{H}_6$  and bisoxazoline ligand **99**, the tricycle **100** was isolated in good yield and high enantioselectivity as shown in **Scheme 29**.



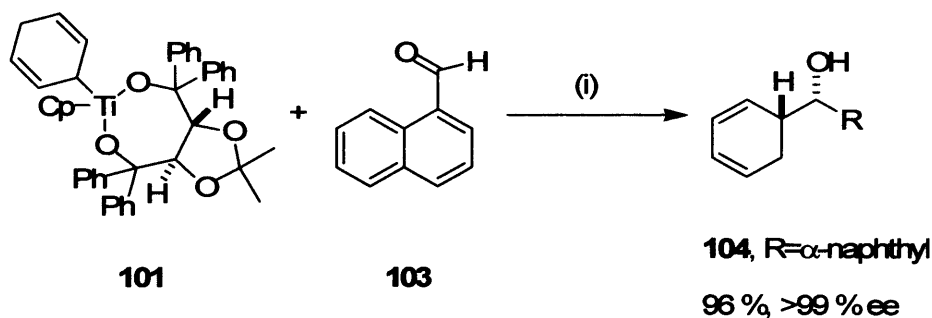
**Scheme 29** Reagents and conditions: (i)  $\text{CuOTf}$  (10 mol %), ligand **99** (15 mol %),  $\text{PhMe}$ , r.t.

#### 1.4.3. Application of chiral metalated cyclohexadiene complexes in asymmetric synthesis

Studer and co-workers<sup>29</sup> demonstrated that derivatisation of 1,4-cyclohexadiene derivatives with chiral metal complexes afforded chiral cyclohexadienyl compounds that undergo stereoselective addition to various aldehydes to provide the corresponding alcohols. Therefore chiral titanium(IV) and chiral boron cyclohexadienyl complexes **101** and **102** respectively were prepared and tested for asymmetric addition to aldehydes. Depending on which double bond of the diene attacks the aldehyde, the two diastereotopic double bonds of the diene would be differentiated and according to which face of the aldehyde would be attacked the enantioselectivity of the addition step could be determined.

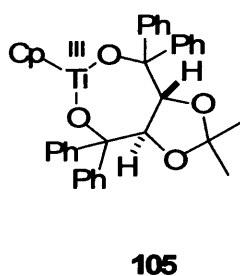


For example chiral Ti-TADDOLate **101** attacked the  $\alpha$ -naphthylaldehyde **103** selectively from the *Si*-face to afford the corresponding 1,3-dienylalcohol **104** with perfect diastereoselectivity and enantioselectivity (dr > 99:1; ee > 99 %) in 96 % yield (**Scheme 30**).



**Scheme 30** Reagents and conditions: (i) THF, T. < -100 °C

The authors noted that these types of reactions have to be conducted at low temperatures (< -100 °C) due to the weakness of the Ti-C bond which homolyses at higher temperatures to give the corresponding chiral Ti(III) complex **105**. However, they showed that these transformations can be used to generate chiral Ti(III) derivatives which can be used in stereoselective pinacol reactions. Moreover, the 1,3-dienes from the addition reactions were used to produce highly important building blocks<sup>30</sup> and utilised as the diene component in intramolecular Diels-Alder reactions.<sup>29a</sup>



## **Chapter 2**

# **Desymmetrisation Strategies – A Starting Point**

[Throughout this chapter, single sulfoxide stereochemistries are indicated by dashes or wedges to indicate the stereogenic centre, but all are racemates. When there is more than one stereogenic centre, the relative stereochemistries proposed are based either on X-ray data and/or mechanistic speculations: in all such cases, the compounds are also racemates].

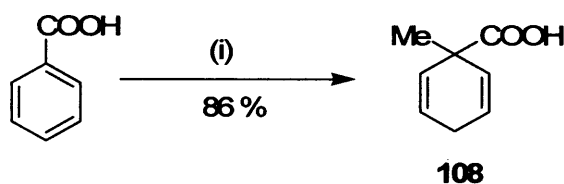
## 2.1. Introduction

To explore the diastereoselectivity of anionic cyclisation onto 1,4-cyclohexadiene rings using chiral sulfoxide methodology, a compound such as **106** was needed. Initially the achiral analogues would be useful to test the key bond-forming reactions without the added stereochemical complexities, and for this purpose a malonate-type nucleophile **107** was selected to give the corresponding cyclised products.



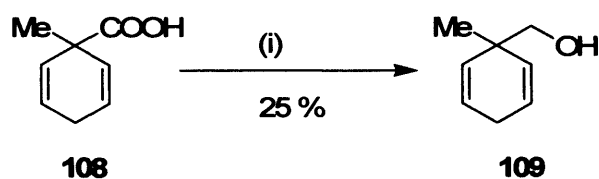
## 2.2. Synthesis and cyclisation of achiral precursors

Since all of the target compounds are 1,4-cyclohexadiene derivatives, the ideal methodology is found in the Birch reduction reaction. In this case, the reduction of benzoic acid<sup>31</sup> with subsequent alkylation at the *ipso* position with iodomethane was carried out to give 1-methyldihydrobenzoic acid **108** with the required quaternary carbon (not yet stereogenic) in high yields.



**Scheme 31** Reagents and conditions: (i) Li, NH<sub>3</sub> (l), -30 °C, then CH<sub>3</sub>I

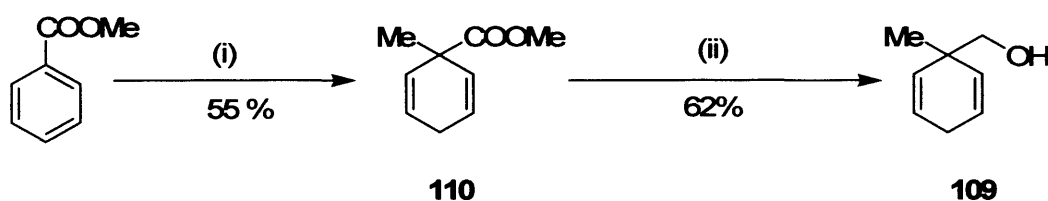
Treatment of crude **108** with ethyl chloroformate in the presence of triethylamine, followed by reduction of the intermediate mixed anhydride with sodium borohydride, afforded the alcohol **109**<sup>32</sup> in 25 % overall yield after purification by flash chromatography as shown in **Scheme 32**.



**Scheme 32** *Reagents and conditions:* (i)  $\text{ClCO}_2\text{Et}$ ,  $\text{Et}_3\text{N}$ , THF,  $-10\text{ }^\circ\text{C}$ ,  $\text{NaBH}_4$ , r.t., 1 h.

The low yield of this intermediate alcohol was considered as an early problem so it was reasonable to find a better method to prepare it. One possibility was using two-step protocol involving initial ester formation followed reduction to the corresponding alcohol.

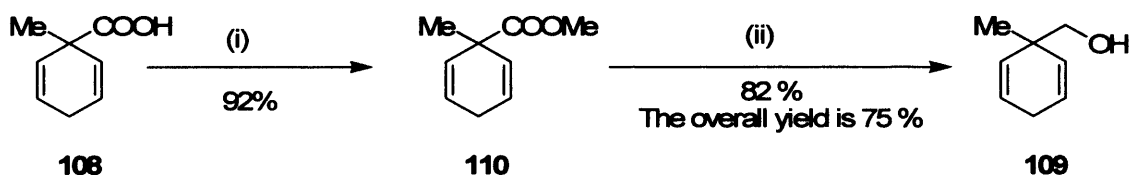
The first method tried was direct Birch reduction of methyl benzoate<sup>33</sup> which afforded ester **110**. Ester **110** was then reduced to the alcohol **109** using sodium borohydride. However, this method was time consuming and a large excess of sodium borohydride (4 equiv.) was required. In addition the obtained alcohol was not pure enough and needed further purification (**Scheme 33**).



**Scheme 33** *Reagents and conditions:* (i) Li,  $\text{NH}_3$  (l), THF, *t*-butanol,  $-30\text{ }^\circ\text{C}$ , then  $\text{CH}_3\text{I}$ ; (ii)  $\text{NaBH}_4$ , EtOH, r.t., 96 h.

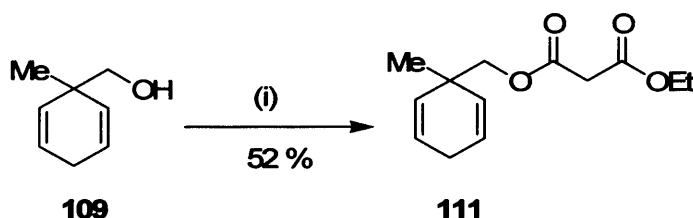
The second method tried was the esterification of acid **108** by a tetrahedral ( $\text{A}_{\text{AC}2}$ ) mechanism to afford ester **110** followed by lithium aluminium hydride reduction.<sup>34</sup> This method gave higher and more reproducible yields in a shorter time and the product was essentially pure and used in the next reactions without further purification (**Scheme 34**).





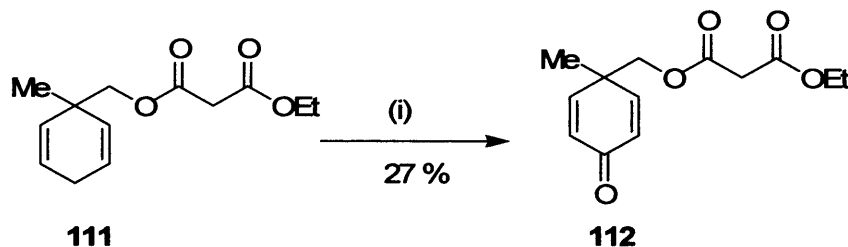
**Scheme 34** *Reagents and conditions:* (i) MeOH, conc. H<sub>2</sub>SO<sub>4</sub>, reflux, 6 h; (ii) LiAlH<sub>4</sub>, THF, r.t., 7 h, 15 % aqueous NaOH, H<sub>2</sub>O, r.t., 17 h.

Introduction of the side chain ester with the functionality required for cyclisation was carried out by reaction of the alcohol **109** with ethyl malonyl chloride in the presence of DMAP and triethylamine to provide mixed malonate ester **111** in moderate yield (**Scheme 35**).



**Scheme 35** *Reagents and conditions:* (i) Ethyl malonyl chloride, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, r.t., 24 h.

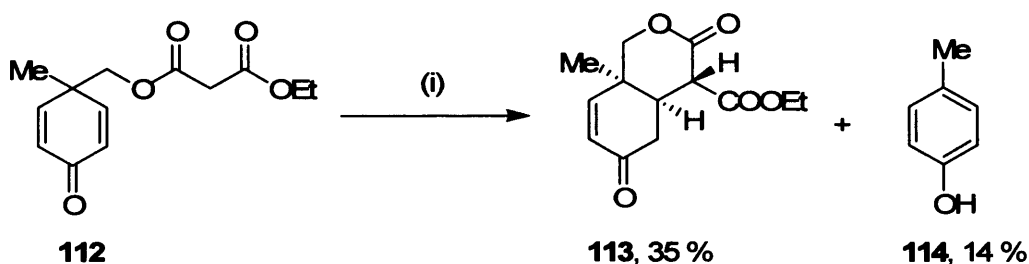
Finally, oxidation of the doubly allylic methylene group of **111** using pyridinium dichromate and *tert*-butyl hydrogen peroxide in benzene<sup>11</sup> was a relatively clean reaction and completely chemoselective, but unfortunately the isolated yield of dienone **112** after chromatography was relatively poor (27%) (**Scheme 36**).



**Scheme 36** *Reagents and conditions:* (i) Benzene, celite, 10 °C, 5 - 6 M solution of *t*-BuOOH in decane, PDC, r.t., 18 h.

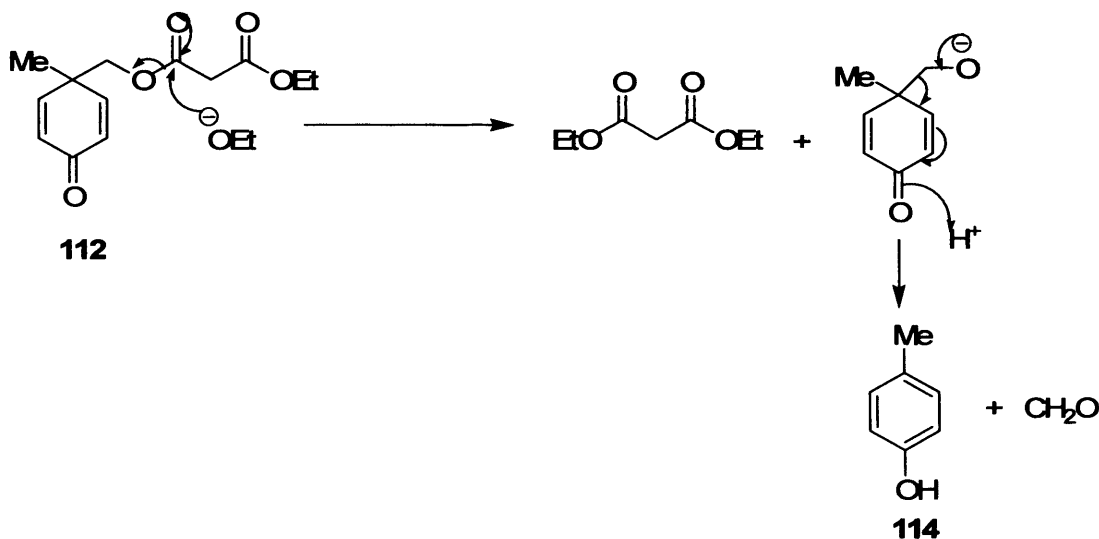
Intramolecular cyclisation of **112** was attempted next. Firstly, the carbon nucleophile was generated by deprotonation of the acidic proton using sodium ethoxide in

ethanol.<sup>35</sup> This method gave a mixture of the desired product **113** in 35 % yield in addition to a significant amount of phenol **114** as a by-product (Scheme 37).



**Scheme 37** Reagents and conditions: (i) 0.5 M NaOEt, EtOH, r.t., 5 h.

This low yield and formation of the by-product presumably due to competition between two reactions as a result of the nucleophilic and basic properties of the ethoxide; acting as a base resulted in formation of the Michael product, while acting as a nucleophile caused transesterification and hydrolysis of the ester side chain followed by deformylation (elimination) of the intermediate alkoxy group which gave rise to the phenol **114**. The driving force for this transformation is to form a more stabilised aromatic compound. Therefore the formation of compound **114** can be rationalised as shown in Scheme 38.



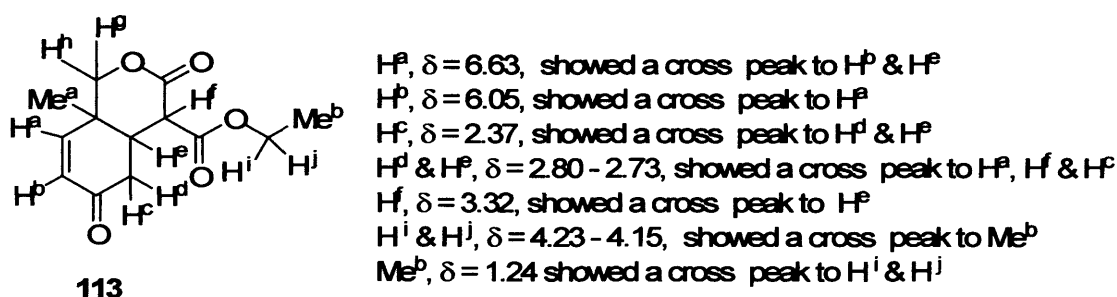
**Scheme 38** The proposed mechanism for the formation of the aromatic by-product

Although cyclisation of dienone **112** could give rise to the formation of four diastereomeric products due to the formation of three new stereogenic centres in one

step, only a single diastereoisomer has ever been observed. This was a very encouraging result.

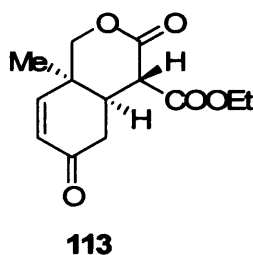
The structure of compound **113** was confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR and  $^1\text{H}$  -  $^1\text{H}$  COSY NMR experiments. Assignment of the structure was based on the following observations. The separation between the protons in the alkene region increased compared to the starting material, indicating formation of a new compound. The presence of two peaks in the alkene region - one of them was a doublet while the other one was a doubled doublet. The smaller dd coupling constant value was 1.6 Hz, which is consistent with a long range W-coupling. The last observation was the presence of a dd peak at  $\delta = 2.3$  ppm. This peak corresponds to one of the two geminal protons ( $\text{H}^c$  and  $\text{H}^d$ ) which indicates the existence of chirality within the molecule. The results of these experiments are summarised in the following diagram.

$^1\text{H}$  -  $^1\text{H}$  COSY experiment showed the following correlations



Coupling constant data are reported in the experimental section.

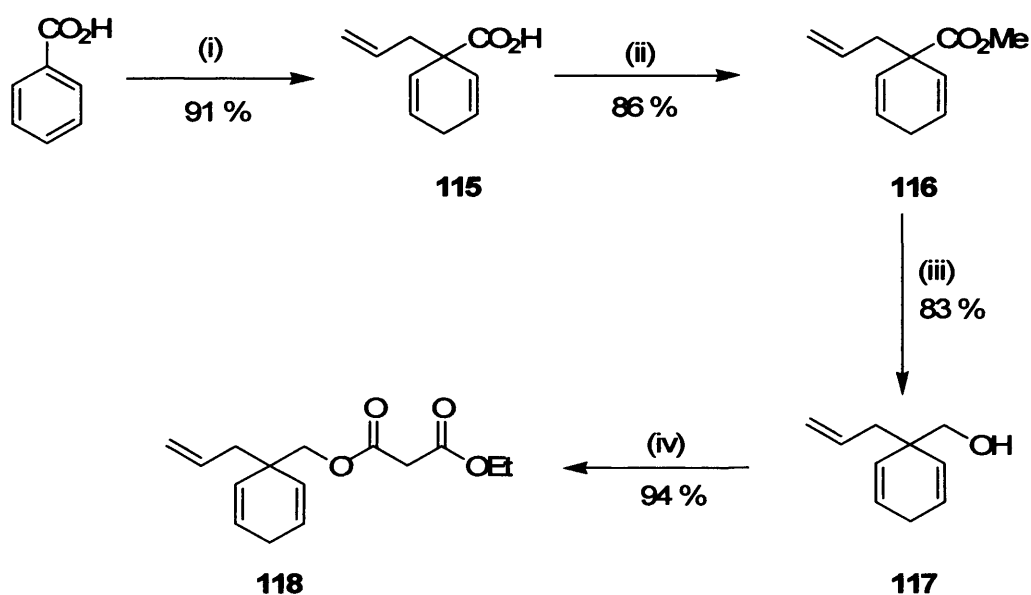
At that point then, determination of the stereochemistry was not a major concern. The more important target was testing the first key cyclisation reaction. However, the relative stereochemistry is assumed to be as shown in the following diagram based on crystal structure data of subsequently prepared compounds.



The key features of this reaction are:

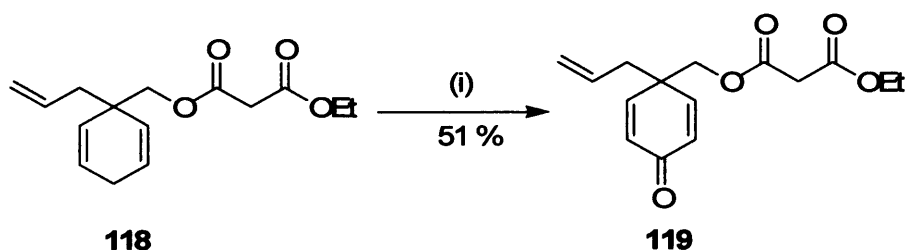
- Formation of a single stereoisomer
- Formation of three stereogenic centres
- Formation of a quaternary stereogenic centre

To define the scope of the reactions other substrates should be examined. Allyl analogues should be easy to prepare. Therefore, acid **115**<sup>11</sup> was prepared in a similar manner to the previous case and elaborated to the mixed malonate ester **118** as shown in **Scheme 39**.



**Scheme 39** *Reagents and conditions:* (i) Li, NH<sub>3</sub> (l), -30 °C, then C<sub>3</sub>H<sub>5</sub>Br; (ii) MeOH, conc. H<sub>2</sub>SO<sub>4</sub>, reflux 24 h; (iii) LiAlH<sub>4</sub>, THF, r.t., 7 h, 15 % aqueous NaOH, H<sub>2</sub>O, r.t., 48 h; (iv) Ethyl malonyl chloride, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, r.t., 24 h

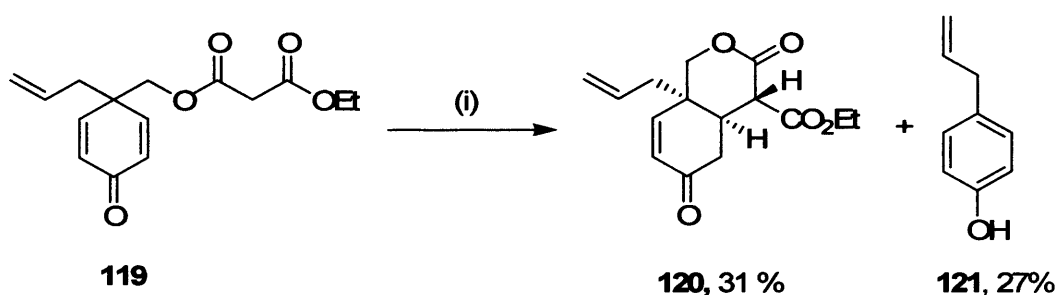
It is noteworthy that oxidation of compound **118** occurred only at the doubly allylic methylene group as desired to give dienone **119** (**Scheme 40**).



**Scheme 40** *Reagents and conditions:* (i) Benzene, celite, 10 °C, 5-6 M solution of *t*-BuOOH in decane, PDC, r.t., 18 h.

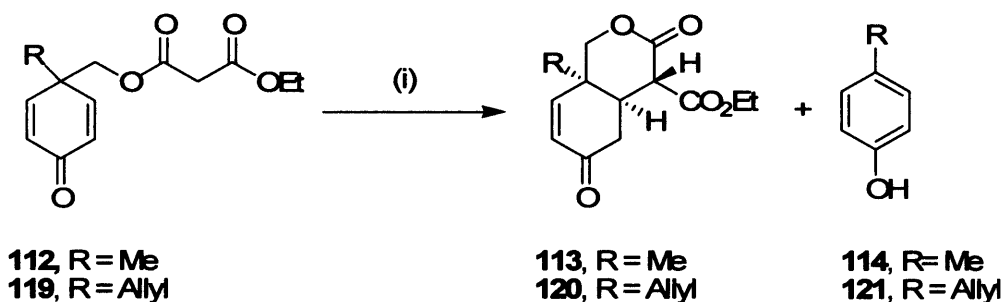
With compound **119** in hand, cyclisation was accomplished exactly as before, giving compound **120** again as a single diastereoisomer in 31 % yield in addition to phenol **121** in 27 % yield as shown in **Scheme 41**.

The structure and stereochemistry of bicyclic compound **120** were proven by 2D NMR spectroscopy and are supported by the crystal structure determination of related compounds as will be explained later.



**Scheme 41** *Reagents and conditions:* (i) EtOH, 0.5 M NaOEt, r.t., 20 h.

As shown in the previous scheme the elimination by- product was formed in a higher yield than in case of the methyl compound at the expense of the desired bicyclic product. In order to suppress this undesired elimination side reaction a bulkier base could be used. In the event, the problem was readily solved by the use of potassium tertiary butoxide in THF to achieve the cyclisation step. This modification in the procedures gave the same products **113** and **120** again as single diastereoisomers, from dienones **112** and **119** respectively. In the case of the methyl compound **112** an extremely high yield was obtained, but with the allyl compound **119** some of the phenol **121** was also formed. This could be due to the presence of traces of water in the reaction mixture as shown in **Scheme 42** and **Table 1**.



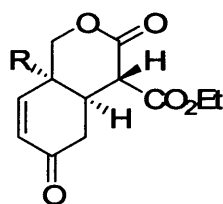
**Scheme 42** Reagents and conditions: (i) KO $t$ -Bu, THF, r.t., 24 - 28 h.

**Table 1**

Substrate	R	Conditions	Yield (compound number) / %
<b>112</b>	CH <sub>3</sub>	NaOEt, EtOH	35 ( <b>113</b> ), 14 ( <b>114</b> )
<b>112</b>	CH <sub>3</sub>	KO $t$ -Bu, THF	92 ( <b>113</b> ), 0 ( <b>114</b> )
<b>119</b>	allyl	NaOEt, EtOH	31 ( <b>120</b> ), 27 ( <b>121</b> )
<b>119</b>	allyl	KO $t$ -Bu, THF	38 ( <b>120</b> ), 8 ( <b>121</b> )

<sup>a</sup> All reactions were carried out at 25 °C.

So far, the intramolecular conjugate addition reactions of cyclohexadienones **112** and **119** were shown to be diastereocontrolled. Although, in principle the cyclisation could give rise to four diastereomeric products (in addition to their enantiomers), only a single diastereoisomer (formed as a racemic mixture since there is no chiral influence) was observed (**Figure 2**).



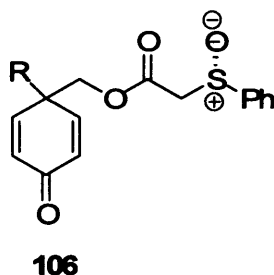
**113**, R = Me  
**120**, R = Allyl

Single stereoisomer  
 3 New stereogenic centres  
 One highly crowded quaternary stereogenic centre  
 No chiral influence  
 Racemic mixture

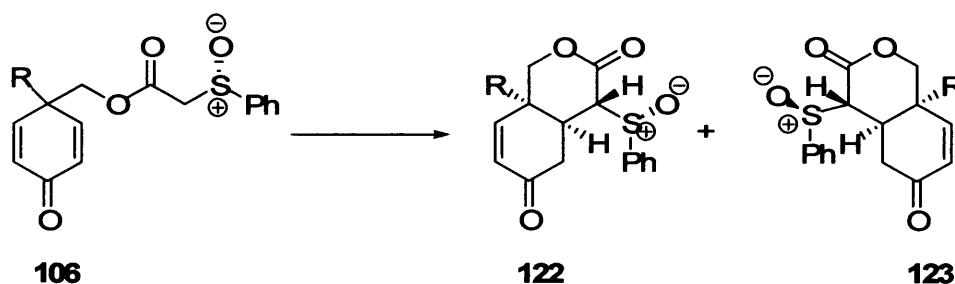
**Figure 2**

### 2.3. Synthesis and cyclisation of chiral sulfoxide precursors

Encouraged by this result, the attention was then turned to build up the suitable precursor **106** with the stereochemical directing chiral sulfoxide in order to investigate the diastereoselectivity of the cyclisation step.



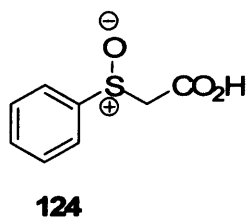
Based on the previous two examples, cyclisation of compound **106** would be expected to give a mixture of diastereoisomers **122** and **123**, where the chiral auxiliary has directed attack towards the diastereotopic double bonds. It was hoped that good selectivity would be obtained, so that one of these two compounds would be favoured over the other (**Scheme 43**).



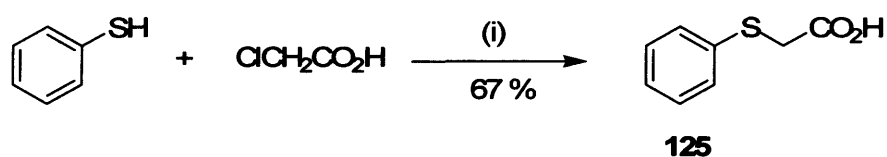
**Scheme 43**

This approach can be investigated with a racemic substrate **106**, giving each diastereoisomer of the products as a racemic mixture.

To synthesise compounds having the general structure **106**, an acid such as **124** was needed.



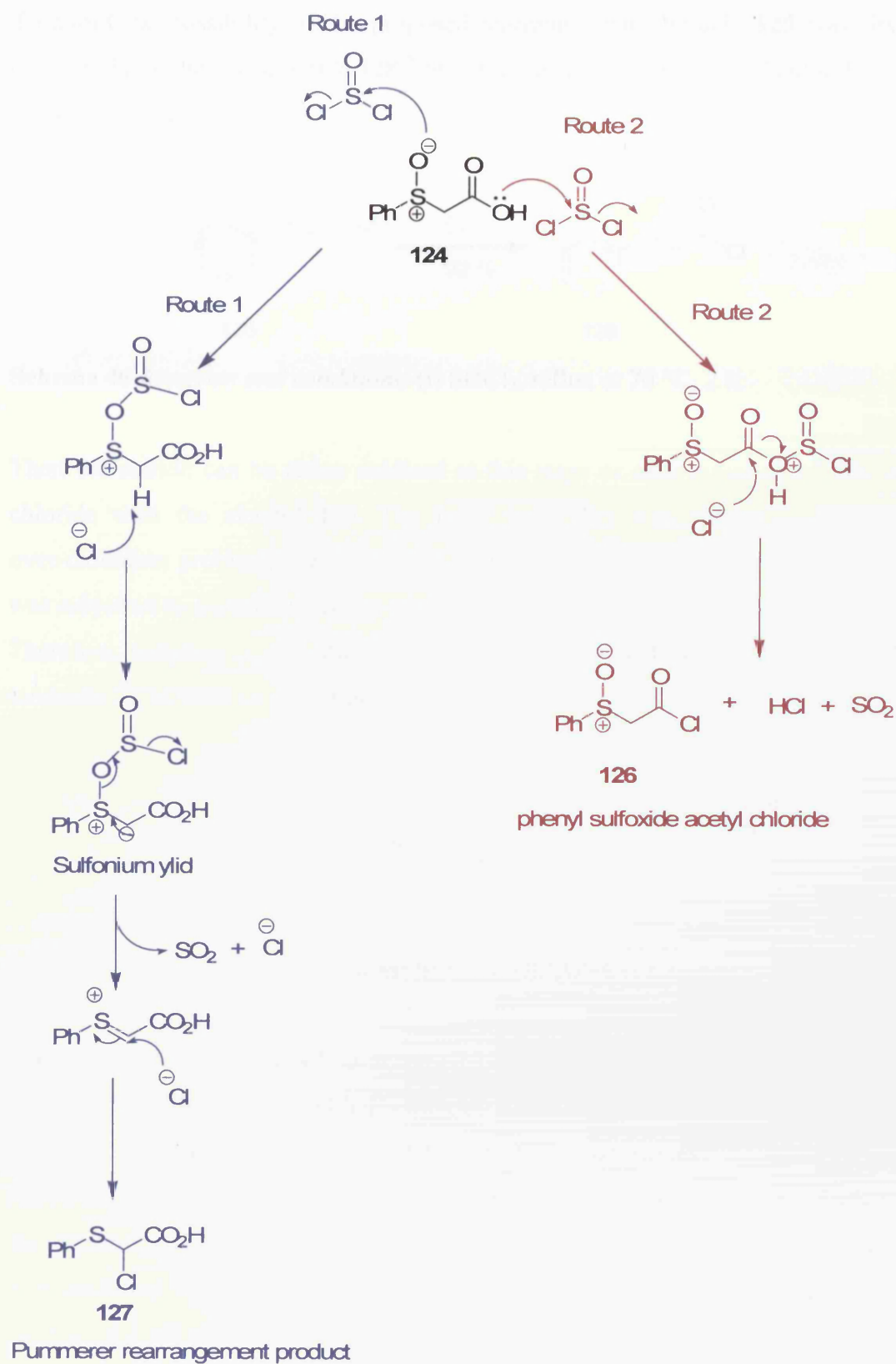
There were no reports of this acid in the literature but its precursor phenylthioacetic acid **125**<sup>36</sup> was known and was prepared by refluxing a mixture of benzenethiol in sodium hydroxide solution with chloroacetic acid for two hours. The reaction mixture was then cooled and acidified with 2 M HCl. The resulting precipitate was filtered and recrystallised from water to afford **125** in 67 % yield.



**Scheme 44** *Reagents and conditions:* (i) Aqueous NaOH, reflux, 2 h.

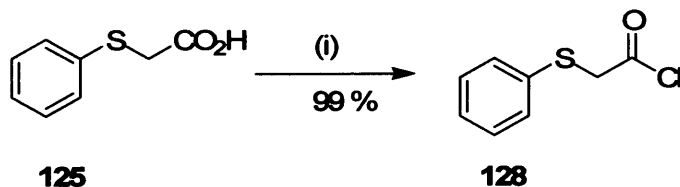
There was a possibility to oxidise the sulfide group in compound **125** selectively to sulfoxide by treating with *m*-chloroperbenzoic<sup>37</sup> acid to afford acid **124** which then can be converted to the corresponding acid chloride **126** by refluxing with thionyl chloride, but these procedures may lead to formation of undesirable product due to the possibility of Pummerer methyl sulfoxide rearrangement as shown in **Scheme 45**.





**Scheme 45**

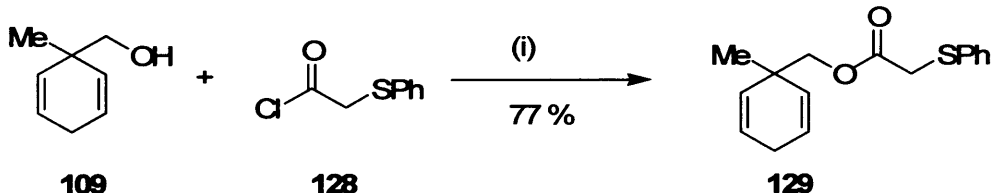
To avoid the possibility of the proposed rearrangement, the acid **125** was firstly converted into the acid chloride **128**<sup>38</sup> by refluxing with excess thionyl chloride at 70 °C for two hours.



**Scheme 46** Reagents and conditions: (i) SOCl<sub>2</sub>, reflux at 70 °C, 2 h.

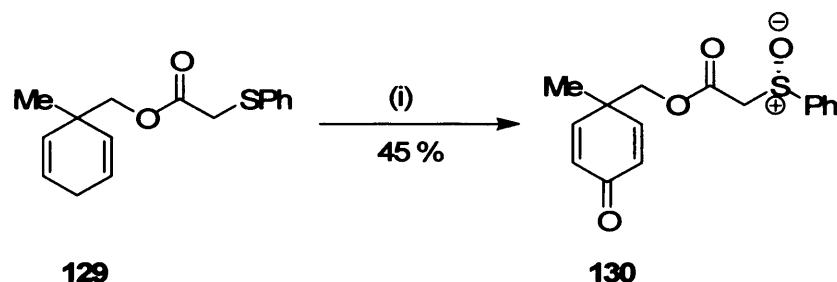
Then the sulfide can be either oxidised at this stage or after coupling of this acid chloride with the alcohol **109**. The latter possibility was chosen to avoid the over-oxidation problems that may arise if the sulfoxide was formed first and then was subjected to another oxidising agent (to effect the allylic oxidation).

Therefore, coupling of this acid chloride with the alcohol **109** afforded ester **129** in moderate 77 % yield as shown in **Scheme 47**.



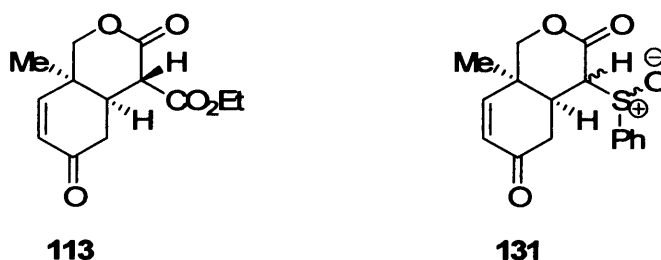
**Scheme 47** Reagents and conditions: (i) Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, r.t., 72 h.

Fortunately oxidation as before accomplished allylic and sulfide oxidation in one step to afford the required chiral sulfoxide **130**. The chirality was clear from the characteristic splitting pattern of the CH<sub>2</sub> next to the oxygen and the CH<sub>2</sub> next to the sulfoxide where each proton is split into a doublet by its geminal proton indicating the diastereotopic nature of these hydrogen atoms. There was no evidence of over-oxidation to the achiral sulfone (**Scheme 48**). Although compound **130** is racemic, the (*S*) stereochemistry will be drawn throughout the following discussion for clarity.



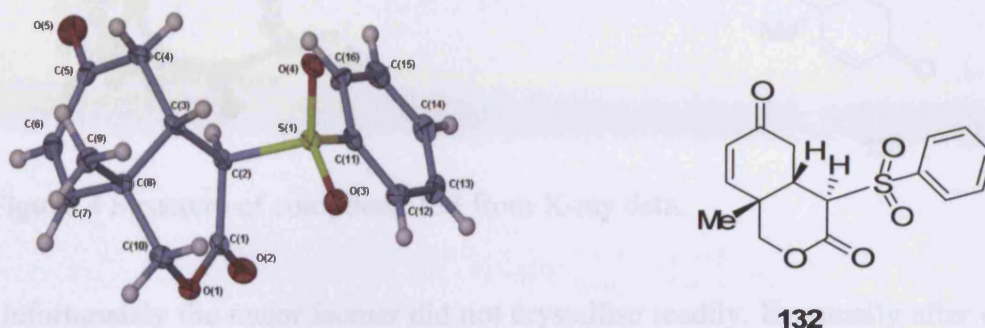
**Scheme 48** *Reagents and conditions:* (i) 5-6 M solution of *t*-BuOOH in decane, PDC, benzene, celite, 0 °C, 2 h., then r.t., 18 h.

Intramolecular cyclisation of the sulfoxide **130** under the standard conditions was attempted next and four compounds were evident from the  $^1\text{H}$  NMR spectrum of the crude reaction mixture. Three of them initially appeared to be isomers of the desired product, as indicated by the similar spectroscopic features compared to that of compound **113**, in addition to an aromatic by product. The ratio of these isomers was 1.00:4.63:8.38.



These compounds were separated by column chromatography and characterised in the first instance by high field NMR spectroscopy. As might be expected, this gave no indication of the relation between the sulfoxide stereochemistry and the three new stereogenic centres formed during the reaction. But it showed that the very minor compound (according to the  $^1\text{H}$  NMR integration), which was the first one to elute from the column after the aromatic decomposition product, has a different splitting pattern for the aromatic protons from those for the other two isomers. In the very minor compound they were well separated while for the other two isomers they were overlapped. Fortunately it crystallised readily, and it was slightly surprising to find that it was a sulfone rather than the sulfoxide as proven from its X-ray structure analysis (**Figure 3**). This compound was formed in variable amounts during the cyclisation. This is somewhat surprising since the oxidation of a sulfoxide to a

sulfone requires relatively forcing conditions. There was no sign in the previous oxidation step of over-oxidation to the sulfone. It seems likely that some oxidation of the minor and the major isomers or possibly only one of them, is occurring upon carrying out the reaction or during the work up.

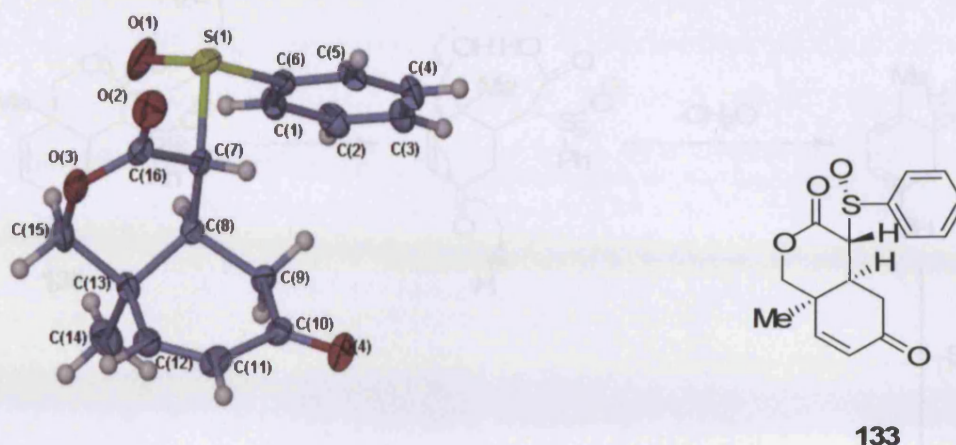


**Figure 3** Structure of compound **132** from X-ray data.

The third compound to elute from the column was the minor isomer followed by the major isomer. The NMR spectrum of the minor showed that one of the CH<sub>2</sub> protons next to carbonyl group in the cyclohexenone ring has a strange chemical shift value of 0.93 ppm which may be caused by the proximity of this proton to the phenyl group which made it subjected to an anisotropic effect and shifted it significantly upfield.

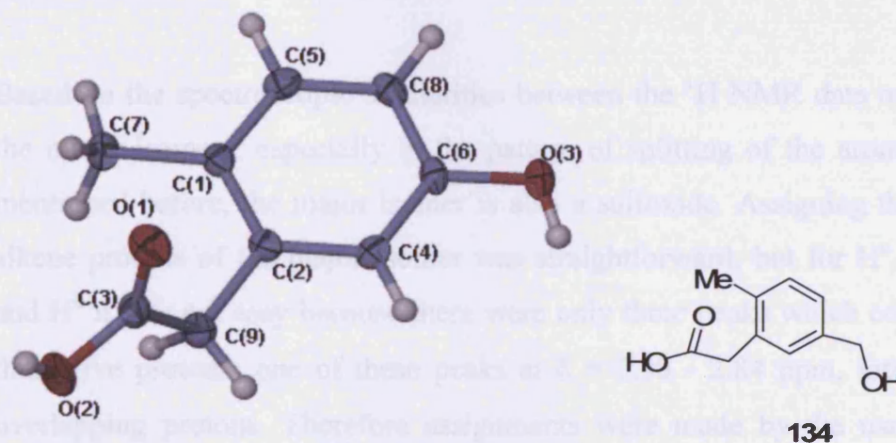
At the beginning it was difficult to form good crystals of the remaining two isomers for X-ray analysis. However, after the reaction was repeated many times, eventually the minor compound crystallised and its structure and stereochemistry were proven by X-ray analysis as shown in **Figure 4**. One of the hydrogen atoms on C(9) is close to the aromatic ring.





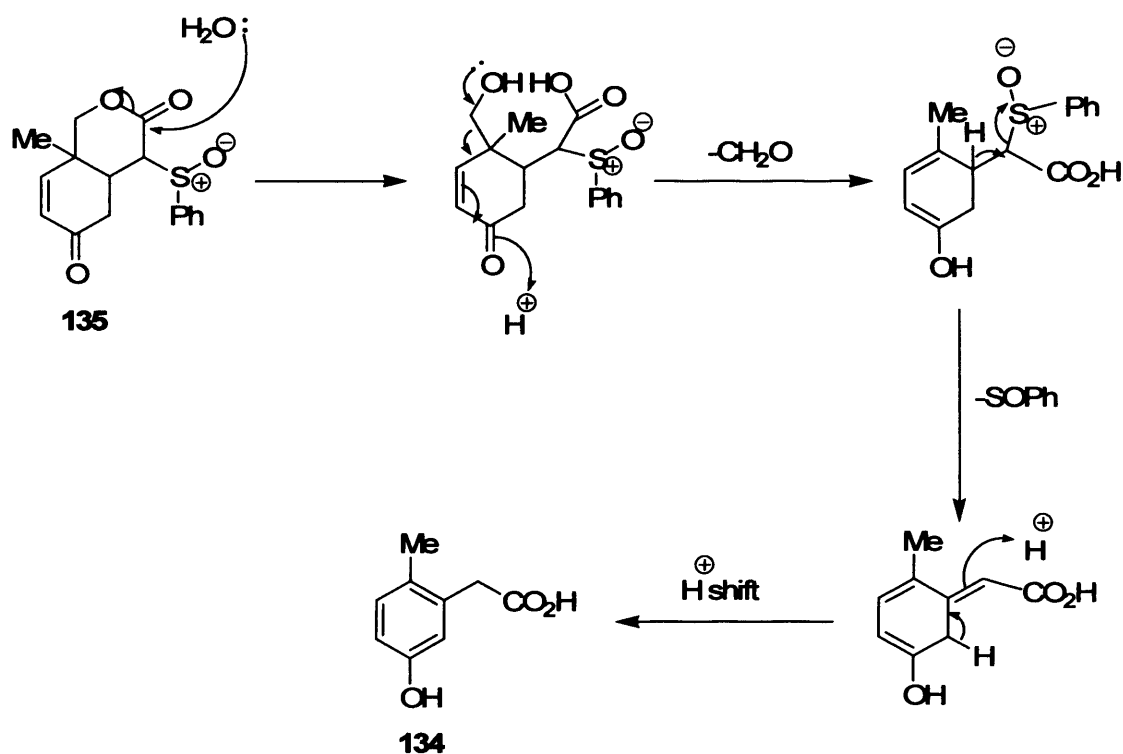
**Figure 4** Structure of compound **133** from X-ray data.

Unfortunately the major isomer did not crystallise readily. Eventually after different solvent systems were used some crystals did form but their X-ray data showed that these crystals are of a decomposition aromatic product **134** as shown in **Figure 5**.



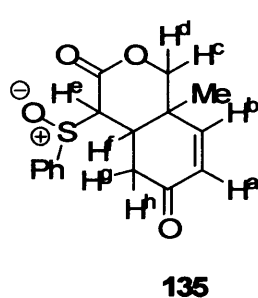
**Figure 5** Structure of compound **134** from X-ray data

It had already been observed that the major compound undergoes a colour change from colourless to yellow upon standing, which may be an indication that this compound is unstable. The proposed mechanism for the formation of this decomposition product is shown in **Scheme 49**.



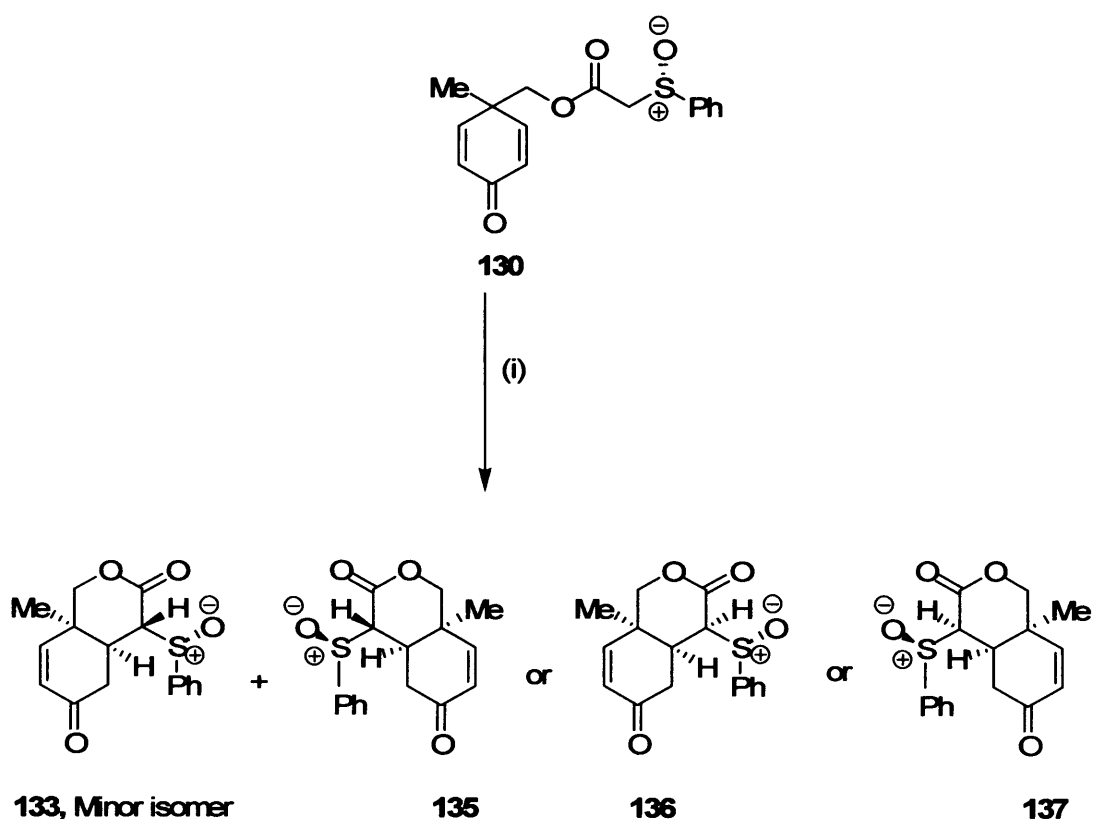
**Scheme 49** The proposed mechanism for the formation of the decomposition product **134**

Based on the spectroscopic similarities between the  $^1\text{H}$  NMR data of the major and the minor isomers, especially in the pattern of splitting of the aromatic protons as mentioned before, the major isomer is also a sulfoxide. Assigning the aromatic and alkene protons of the major isomer was straightforward, but for  $\text{H}^c$ ,  $\text{H}^d$ ,  $\text{H}^f$  and  $\text{H}^g$  and  $\text{H}^h$  it was not easy because there were only three peaks which could account for these five protons; one of these peaks at  $\delta = 2.90 - 2.84$  ppm, integrates to three overlapping protons. Therefore assignments were made by the use of a  $^1\text{H} - ^1\text{H}$  COSY experiment as summarised in the following diagram.



$\text{H}^a$ ,  $\delta = 6.54$ , showed cross peak to  $\text{H}^b$  &  $\text{H}^f$   
 $\text{H}^b$ ,  $\delta = 6.03$ , showed cross peak to  $\text{H}^a$   
 $\text{H}^c$ ,  $\delta = 3.86$ , showed cross peak to  $\text{H}^f$  (one of the protons at  $\delta = 2.90 - 2.84$ )  
 $\text{H}^d$ ,  $\delta = 2.47$ , showed cross peak to  $\text{H}^h$  &  $\text{H}^f$  (two of the protons at  $\delta = 2.90 - 2.84$ )  
 $\text{H}^e$ ,  $\text{H}^f$  &  $\text{H}^g$   $\delta = 2.90 - 2.84$ , showed cross peak to  $\text{H}^a$ ,  $\text{H}^d$  &  $\text{H}^b$   
 $\text{H}^h$ ,  $\delta = 3.75$ , showed cross peak to  $\text{H}^c$  (one of the protons at  $\delta = 2.90 - 2.84$ )

The previous experiments confirmed the structure but did not explain the relative stereochemistry of the major isomer. Also, nOe experiments did not help due to the overlap between three different protons as explained before. Theoretically, upon cyclisation of compound **130** three new stereogenic centres will be formed so in principle eight diastereoisomers (each existing as a pair of enantiomers) could be formed. In fact, only two diastereoisomers were formed, in a 2:1 ratio. The cyclisation reaction is extremely unlikely to give a *trans* ring junction, so that at this stage the major isomer could be one of three structures (**135**, **136** or **137** since **133** is the minor diastereoisomer) as shown in **Scheme 50**.



**Scheme 50** *Reagents and Conditions*: (i) THF, KOt-Bu, 0 °C, 5.5 h, then r.t., 17.5 h.

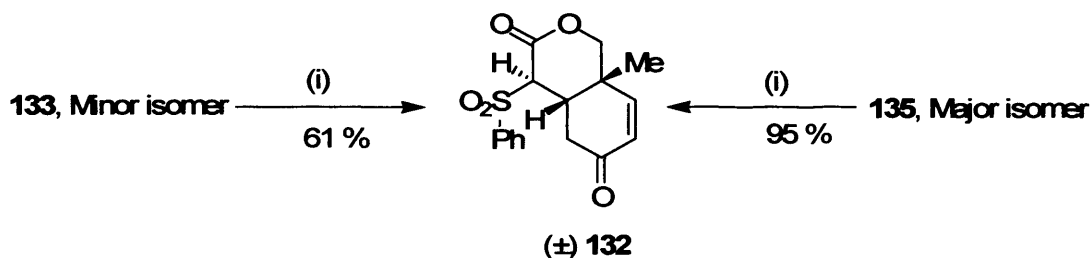
Isomer **136** would be due to attack on the same double bond as in the minor compound **133**, so that if compound **136** is the major isomer this would mean that the sulfoxide is able to completely discriminate between the two double bonds. However, in the case of structures **135** and **137** they would result from attack on the other double bond.

Since the cyclisation of achiral dienone **112** was diastereocontrolled and gave only one stereoisomer, it is very likely that the relative stereochemistry of the major and the minor isomers in this case is the same at the three carbon stereogenic centres. That is, the major isomer is most likely to be structure **135**.

The X-ray structure of both the minor isomer **133** and the sulfone **132** indicated that they have the same relative stereochemistry at all the three carbon-stereogenic centres. Again, it seemed reasonable to assume at this stage that the major isomer (*i.e.* **135**) also has this same relative stereochemistry at all three carbon- stereogenic centres.

If the chirality of the sulfur in both the major and the minor isomers is destroyed by oxidation to the sulfone using oxone<sup>39</sup> in methanol, they should both give the same compound **132**. However, if a different sulfone was formed it would mean that the two isomers have different stereochemistry at one or more of the other three carbon stereogenic centres.

When the major and the minor isomers were oxidised into the sulfone separately they indeed gave the same sulfone (**Scheme 51**).



**Scheme 51** *Reagents and Conditions:* (i) 49.5 %  $\text{KHSO}_5$  in  $\text{H}_2\text{O}$ ,  $\text{MeOH}$ ,  $0^\circ\text{C}$ , r.t., 4 h.

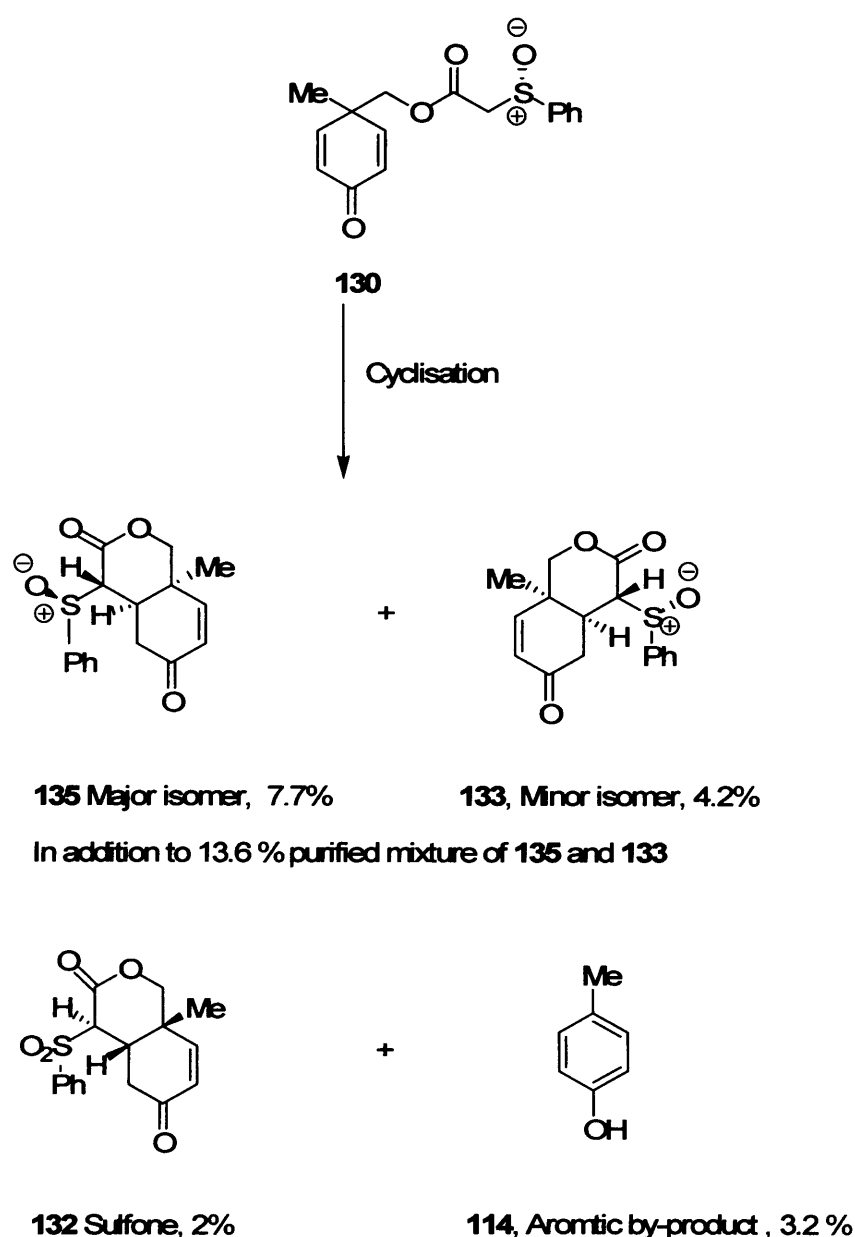
To avoid the possibility that under the reaction conditions the major isomer is epimerised to the minor and then converted into the sulfone, 50 % conversion of a mixture of both isomers was subjected to the previous oxidation. The result was a mixture of the same sulfone and some unreacted minor and major isomers. Therefore the major isomer is confirmed as **135**.

Based on this assumption, the stereochemistry of compound **113** has assigned as previously drawn. The assignment of the stereochemistry of compound **135** is also



supported by a crystal structure determination of the major isomer from a subsequent related reaction (*vide infra*).

At that point then, it was established that the two sulfoxide isomers **133** and **135** differed in the choice of double-bond attacked so that if a single enantiomer at sulfur was used, the difference between the major and the minor isomers will be at all three new stereogenic centres. So it can be concluded that the stereochemistry of the cyclisation reaction has been controlled as hoped, by the chiral sulfoxide and this allowed us to distinguish between the two diastereotopic double bonds (2:1 ratio). The results and the yields obtained are summarised in **Scheme 52**.

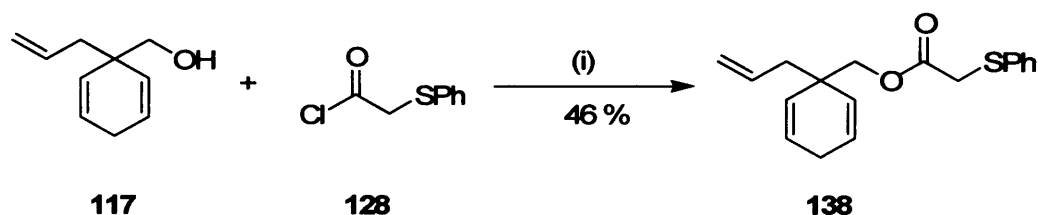


**Scheme 52** *Reagents and Conditions:* (i) KOt-Bu, THF, 0 °C, 5.5 h., then r.t., 17.5 h.

The isolated yields were very low due to losses on purification. The purification process took long time to separate the four compounds in a pure form suitable for characterisation. The main problem was due to both the major and the minor isomers have very close  $R_f$  values so, the repeated purification was required.

Regardless of this problem, the cyclisation reaction can be considered very successful. It allowed us to test the idea of desymmetrisation between the two diastereotopic double bonds of 1,4-cyclohexadiene derivatives under the influence of a chiral sulfoxide with simultaneous formation of a highly crowded quaternary stereogenic centre in addition to another two vicinal stereogenic centres in a single step.

To check how general the diastereoselective cyclisation of cyclohexa-1,4-dienes under the influence of chiral sulfoxide is, the previous reactions were repeated using alcohol **117** to form ester **138** (Scheme 53).

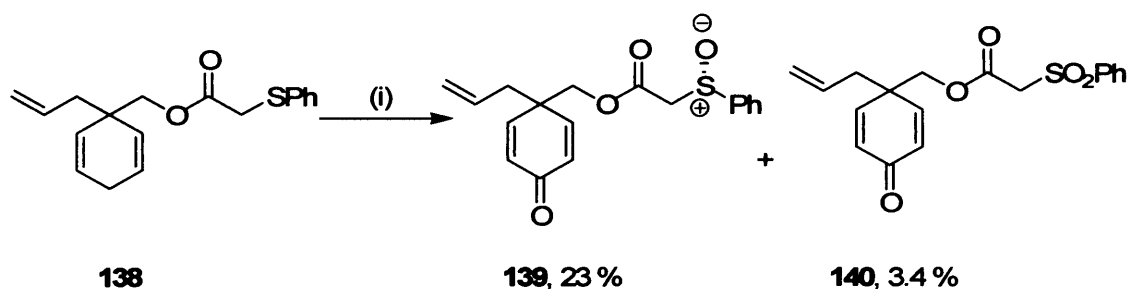


**Scheme 53** *Reagents and Conditions:* (i)  $Et_3N$ , DMAP,  $CH_2Cl_2$ , r.t., 13 days

It was difficult to obtain satisfactory mass spectrometric data for sulfanyl cyclohexadiene **138** as this sulfide was ready oxidised upon carrying out the low resolution experiment and gave a peak corresponding to  $MH^+ + O$ . The high resolution data were therefore not recorded.

Oxidation of the ester **138** under the standard conditions gave the desired sulfoxide dienone **139** and sulfone dienone **140**. This was the first time a sulfone was observed in the oxidation step. Assignment the structure of this sulfone was based on the following observations. Disappearance of the doubly allylic methylene group was accompanied by shifting of the alkene protons to higher chemical shift indicated allylic oxidation. Absence of any sign of chirality in the molecule (all the  $CH_2$  groups

were singlets, but shifted to a higher chemical shift), and the aromatic protons were well separated indicated sulfone rather than sulfide (**Scheme 54**).



**Scheme 54 Reagents and Conditions:** (i) 5-6 M solution of *t*-BuOOH in decane, PDC, 2 h, benzene, celite, 0 °C, then r.t., 18 h.

Cyclisation of substrate **139** proceeded in a similar manner to give four compounds with similar spectroscopic features to those produced from the cyclisation of compound **130**. In this case the major isomer crystallised readily, and its stereochemistry was found to be the same as that deduced for the major isomer resulted from the cyclisation of compound **130** (**Figure 6** and **Scheme 55**), confirming our previous assignment (Note that the absolute stereochemistry at sulfur in the crystal structure of compound **141** is opposite to that observed for compound **133**. This is a result of choice of crystals from a racemic mixture. The stereochemistry at sulfur in the reaction schemes has been drawn as (*S*) throughout for consistency and clarity).

While the ratio of the products in the crude reaction mixture is essentially identical to that observed in the previous reaction, the products are not as pure as those obtained in the previous reaction. This is due to the presence of a small amount of the starting material in the crude reaction mixture.

To improve the selectivity the reaction was repeated as before but at 0 °C. However, the <sup>1</sup>H NMR spectrum of the crude reaction mixture showed the same major and minor products.

The reaction was repeated as before but with the use of a different solvent, THF, and the same results were obtained.

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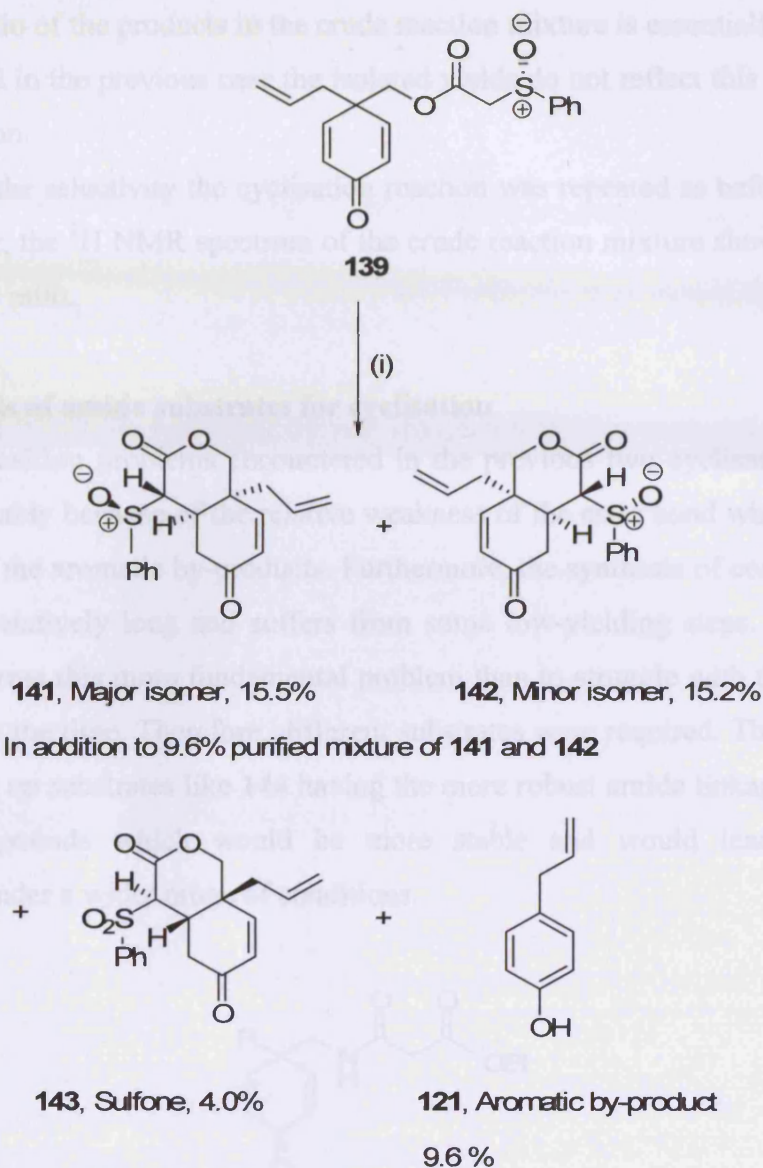
The reaction was repeated as before but with the use of a different solvent, THF, and the same results were obtained.

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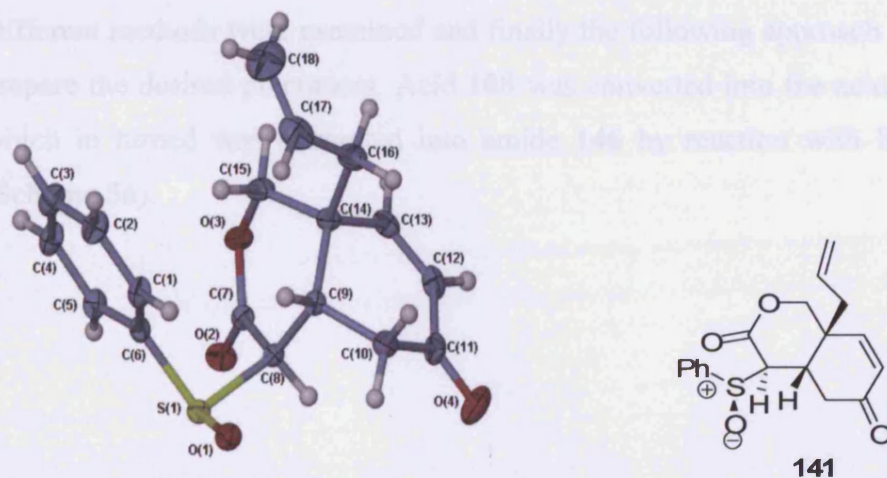
The reaction was repeated as before but with the use of a different solvent, THF, and the same results were obtained.

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**Scheme 55** Reagents and Conditions: (i) KO<sup>t</sup>-Bu, THF, 0 °C, 3.5 h, then r.t., 14 h.



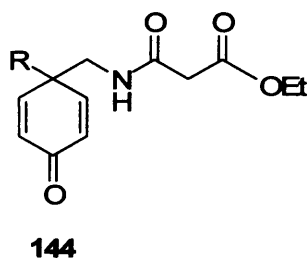
**Figure 6** Structure of compound **141** from X-ray data

While the ratio of the products in the crude reaction mixture is essentially identical to that observed in the previous case the isolated yields do not reflect this due to losses on purification.

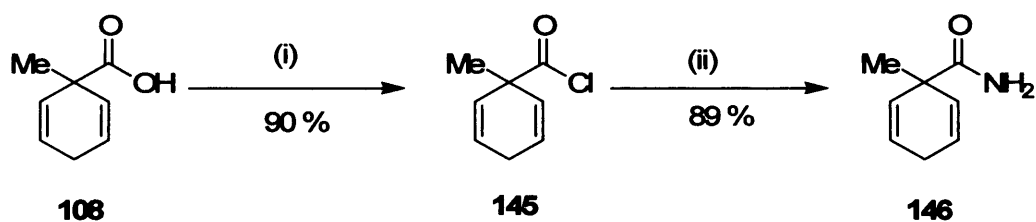
To improve the selectivity the cyclisation reaction was repeated as before but at -20 °C. However, the  $^1\text{H}$  NMR spectrum of the crude reaction mixture showed the same major: minor ratio.

#### 2.4. Synthesis of amide substrates for cyclisation

The decomposition problems encountered in the previous two cyclisation reactions were presumably because of the relative weakness of the ester bond which led to the formation of the aromatic by-products. Furthermore, the synthesis of compounds **130** and **139** is relatively long and suffers from some low-yielding steps. Thus, it was better to address this more fundamental problem than to struggle with this particular cyclisation at the time. Therefore, different substrates were required. The first choice was building up substrates like **144** having the more robust amide linkage in order to deliver compounds which would be more stable and would lead to cleaner cyclisation under a wider range of conditions.

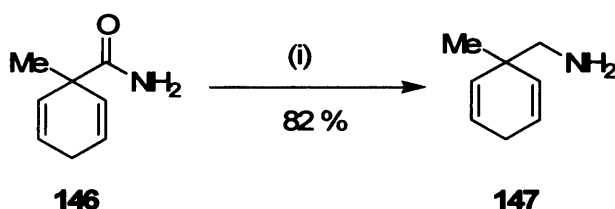


Different methods were examined and finally the following approach was adopted to prepare the desired precursors. Acid **108** was converted into the acid chloride **145**<sup>31</sup> which in turned was converted into amide **146** by reaction with liquid ammonia (**Scheme 56**).



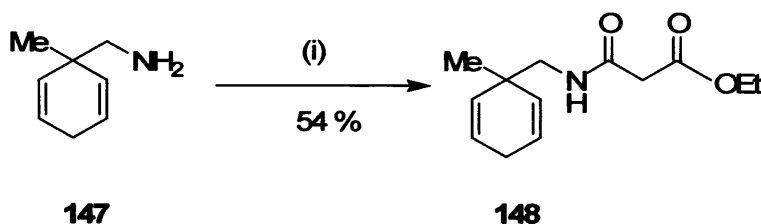
**Scheme 56 Reagents and Conditions:** (i)  $\text{SOCl}_2$ , reflux, 2 h.,  $70^\circ\text{C}$ ; (ii)  $\text{NH}_3(\text{l})$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 1.5 h., r.t., 18 h.

Reduction of the amide **146** using lithium aluminium hydride afforded amine **147** in 82 % yield (**Scheme 57**).



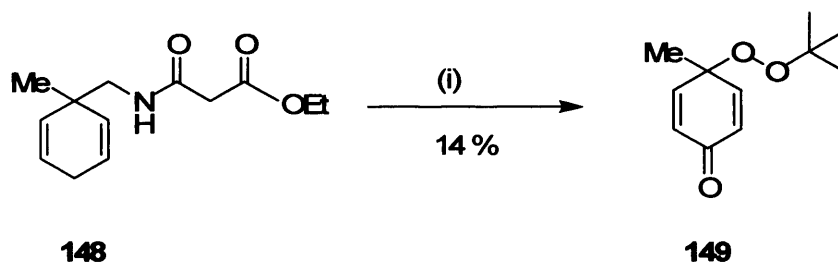
**Scheme 57 Reagents and Conditions:** (i)  $\text{LiAlH}_4$ , THF, r.t., 2 h., reflux, 24 h., r.t., 15 % aqueous  $\text{NaOH}$ ,  $\text{H}_2\text{O}$ , r.t., 72 h.

Coupling amine **147** with ethyl malonyl chloride gave amido ester **148** in 54 % yield (**Scheme 58**).



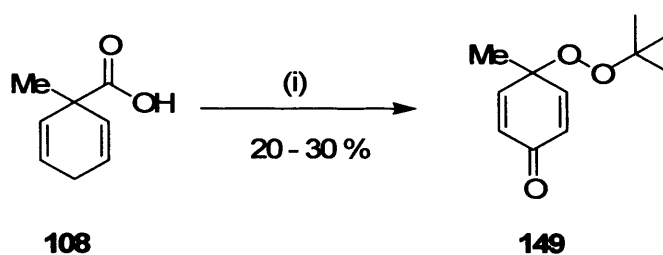
**Scheme 58 Reagents and Conditions:** (i) Ethyl malonyl chloride,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ , r.t., 66 h.

Oxidation of amido ester **148** was attempted next, but unfortunately this resulted in formation of unexpected peroxide **149** (**Scheme 59**).



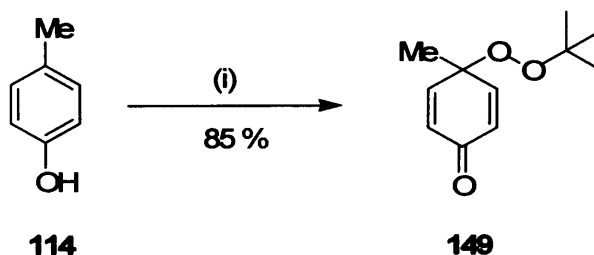
**Scheme 59** *Reagents and Conditions:* (i) 5-6 M solution of *t*-BuOOH in decane, PDC, benzene, celite, r.t., 24 h.

Assignment of the structure of this peroxide was mainly based on  $^1\text{H}$  and  $^{13}\text{C}$  NMR data. The  $^{13}\text{C}$  NMR spectrum of the purified fractions revealed the following features. The presence of a ketone group and two alkene CH groups with chemical shift values higher than those for simple alkenes, indicating that they are conjugated with the ketone group. The presence of two quaternary carbon atoms of very high chemical shift values, indicating that they are attached to a heteroatom. In addition to the presence of two  $\text{CH}_3$  groups with different intensities indicating that one of them may correspond to more than one  $\text{CH}_3$  group. Although the  $^1\text{H}$  NMR spectrum was very simple with only four peaks, it helped to confirm the structure. The first two peaks were at chemical shift values of  $\delta = 6.83$  and  $6.15$  ppm. Each peak was a doublet and integrates to two protons. The remaining two peaks were singlets at chemical shift values of  $\delta = 1.32$  and  $1.13$  ppm. The first of these integrates to three protons while the second one integrates for nine protons. After initially suggesting the structure, a literature search was carried out which showed that this peroxide was obtained under similar reaction conditions (1:1 molar mixture of 90 % *t*-BuOOH and PDC) from oxidation of 1-methyl-cyclohexa-2,5-dienecarboxylic acid **108** as an undesirable product as shown in **Scheme 60**.<sup>40</sup>



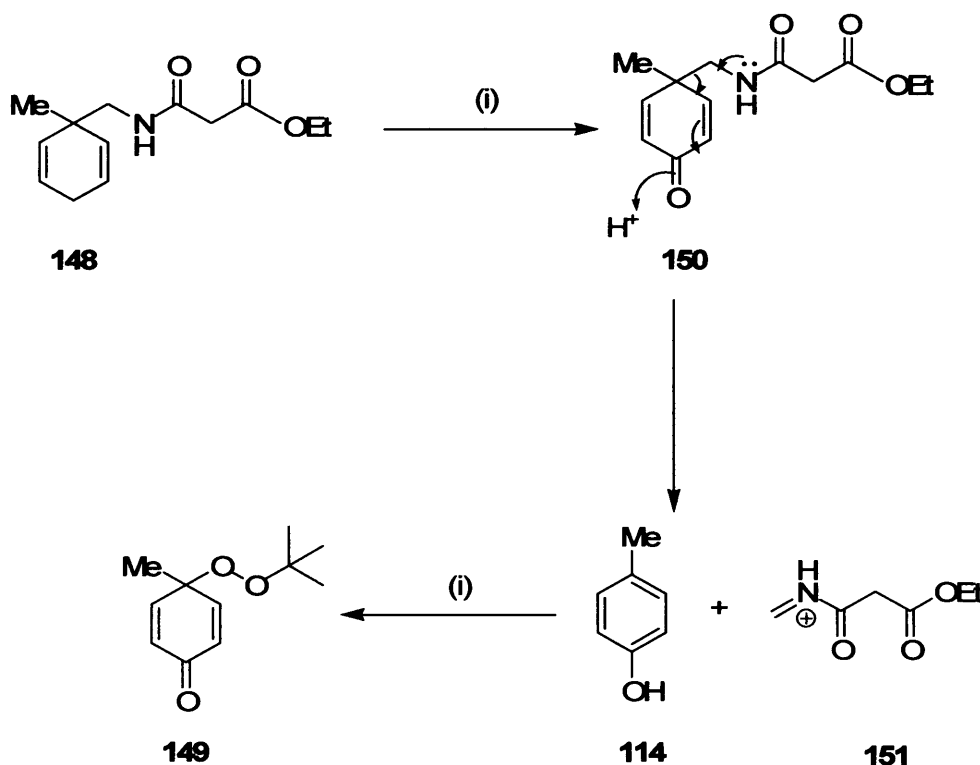
**Scheme 60** *Reagents and Conditions:* (i) 90 % *t*-BuOOH, PDC, dry benzene, celite,  $10^\circ\text{C}$ , 30 min, and then r.t., 4 h.

Also this peroxide was obtained upon oxidation of *p*-cresol with *t*-BuOOH in the presence of a catalytic amount of low-valent ruthenium complex  $\text{RuCl}_2(\text{PPh}_3)_3$ .<sup>41</sup>



**Scheme 61** *Reagents and Conditions:* (i) **114**, EtOAc,  $\text{RuCl}_2(\text{PPh}_3)_3$ , 3.3 M solution of *t*-BuOOH in dry benzene, r.t., 5 h.

The data for compound **149** as obtained from the oxidation of compound **148** were in line with those reported by Murahashi.<sup>41</sup> Presumably **149** is formed *via* oxidative fragmentation of compound **150** as proposed in **Scheme 62**.

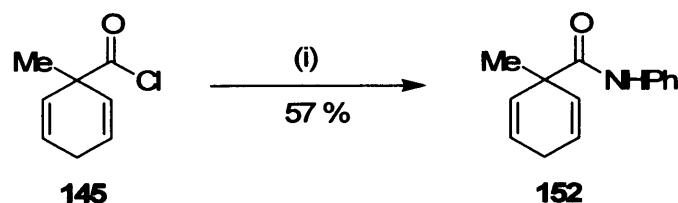


**Scheme 62** (i) 5-6 M solution of *t*-BuOOH in decane, PDC, benzene, celite, r.t., 24 h.

Formation of peroxide **149** was extremely surprising. It can be speculated that it might be due to the presence of a free amide NH in compound **148**. In order to test



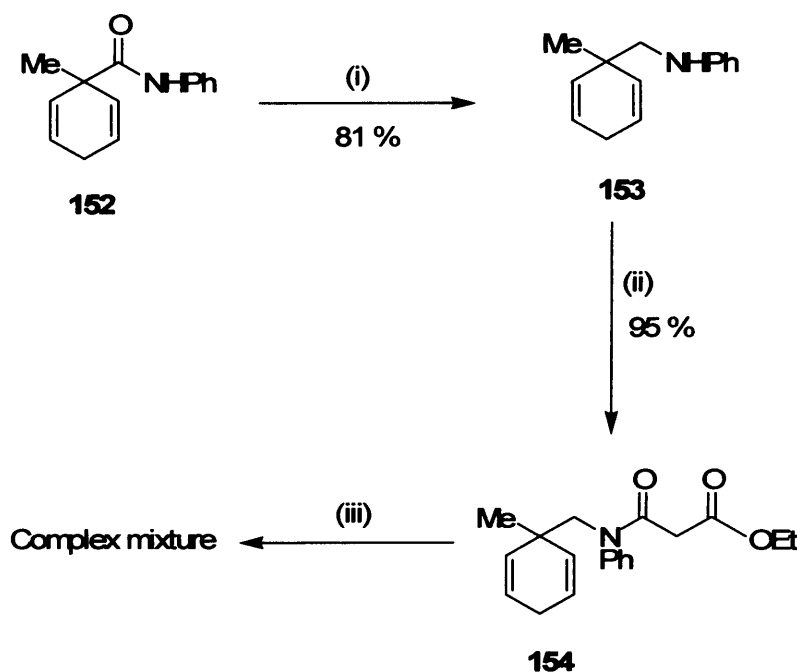
this hypothesis the *N*-phenyl analogue of **148** was prepared as follows. The acid chloride **145** was reacted with aniline to form secondary amide **152**



**Scheme 63** *Reagents and Conditions:* (i) PhNH<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, **145**, DMAP, r.t., 24 h.

To form the side chain needed for the cyclisation, secondary amide **152** was deprotonated using sodium hydride and allowed to react with ethyl malonyl chloride but after stirring the reaction mixture for 18 h, the crude reaction mixture was actually a mixture of the starting materials. Even after repeating the reaction by deprotonation and addition of the acid chloride at 0 °C then refluxing the reaction mixture for 48 hours it did not work.

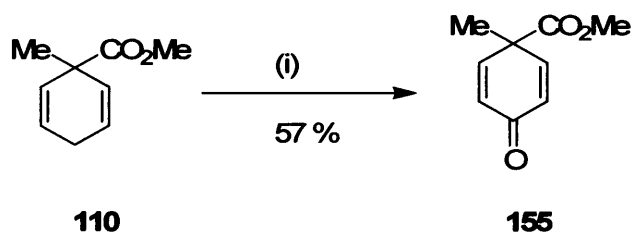
Therefore, the secondary amide **152** was reduced first by LiAlH<sub>4</sub> to provide the secondary amine **153**, which then converted into the tertiary amide **154** by coupling with ethyl malonyl chloride. Again the oxidation step under the standard conditions was problematic and gave a complex mixture (**Scheme 64**).



**Scheme 64** *Reagents and Conditions:* (i)  $\text{LiAlH}_4$ , THF, r.t., 5 days, 15 % aqueous NaOH,  $\text{H}_2\text{O}$ , r.t., 3h; (ii) Ethyl malonyl chloride,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ , r.t., 24 h; (iii) 5-6 M solution of *t*-BuOOH in decane, PDC, benzene, celite, r.t., 24 h.

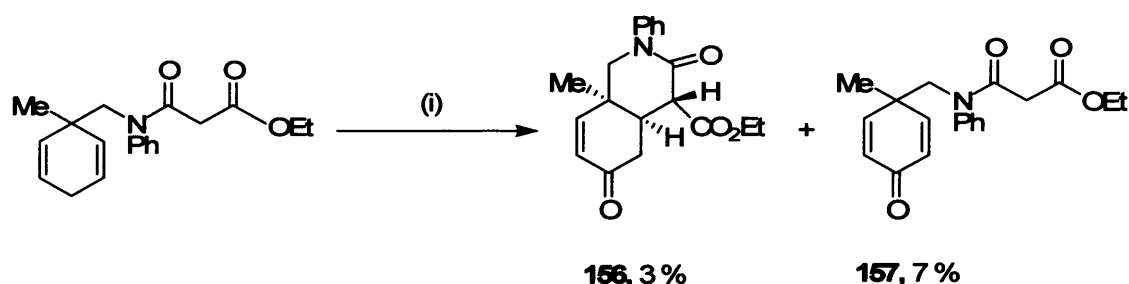
To solve the problem of the allylic oxidation, a literature survey was carried out and many different methods were found, most of them were chromium based.<sup>38,42</sup> As an alternative, selenium dioxide in dioxane at 80 °C<sup>43</sup> was tried but this resulted in starting material being recovered unchanged.

Back to the use of chromium as the oxidising metal, another method was tested upon a simpler substrate **110**. This method involves refluxing the substrate with PDC in ethanol-free chloroform.<sup>42a</sup> It worked very well giving compound **155** as essentially pure oil in 57 % yield without any indication of side decomposition reactions.



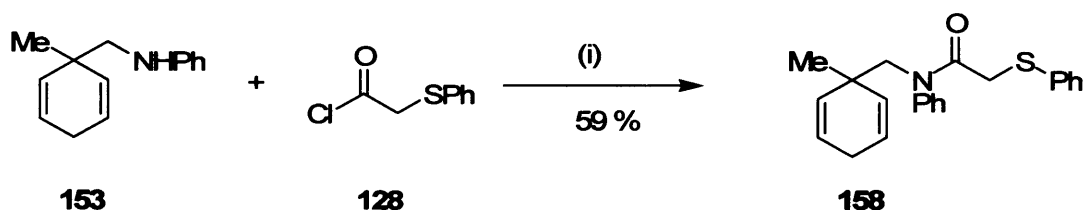
**Scheme 65** *Reagents and Conditions:* (i) PDC, 4Å-molecular sieves, EtOH-free  $\text{CHCl}_3$ , reflux, 24 h.

When this method was attempted with amidoester **154** it did work and some of the desired dienone **156** was isolated after purification, but the yield was very poor (less than 5 %). It appears that these substrates are difficult to oxidise. However, before giving up on these compounds this method was repeated under different reaction times and the best result was obtained after refluxing for 3.5 h. Purification of the reaction mixture by flash chromatography afforded amidodienone **157** in 7 % yield and the cyclised final product **156** in 3 % yield as evident by comparing the  $^1\text{H}$  NMR spectrum of the isolated fractions with that of compound **113**. Compound **156** could not be fully characterised due to the small amounts isolated (**Scheme 66**).



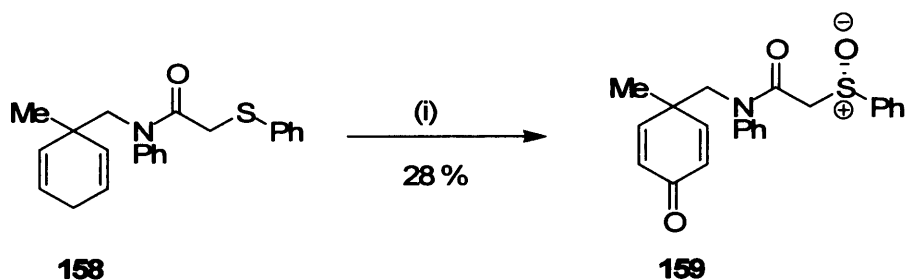
**Scheme 66 Reagents and Conditions:** (i) PDC, 4Å-Molecular sieves, EtOH-free  $\text{CHCl}_3$ , reflux, 3.5 h.

If a good method for the oxidation could be found it seems very likely that cyclisation would be successful. Therefore, the sulfide analogue of **158** was prepared as shown in **Scheme 67**.



**Scheme 67 Reagents and Conditions:** (i)  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ , r.t., 72 h.

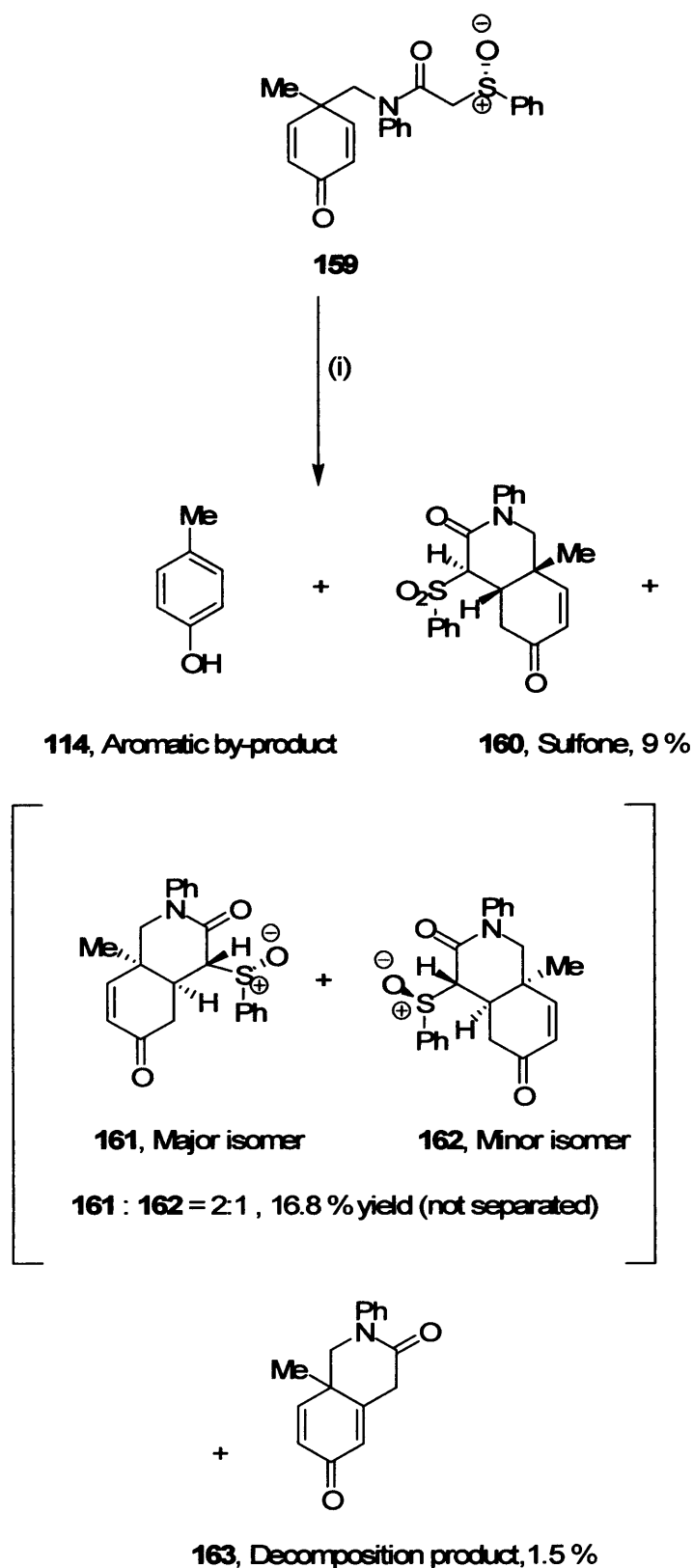
Oxidation of substrate **158** using standard conditions afforded compound **159** in 23 % yield. Using milder conditions<sup>34</sup> PDC in  $\text{CH}_2\text{Cl}_2$ , at  $-20\text{ }^\circ\text{C}$  in the presence of 70 % aqueous solution of *t*-BuOOH afforded a clean reaction and slightly improved the yield to 28 %.



**Scheme 68** *Reagents and Conditions:* (i) PDC, 70% aqueous solution of *t*-BuOOH, CH<sub>2</sub>Cl<sub>2</sub>, -20 °C, 48 h.

Cyclisation of **159** was attempted next using sodium hydride, but unfortunately it gave the same products sulfone, major, minor and aromatic decomposition product, having the same spectroscopic features as those obtained upon cyclisation of compounds **130** and **139**, with a major:minor ratio of 2:1 (according to the integration in the <sup>1</sup>H NMR spectrum of the crude reaction mixture). However the major isomer resulted from this cyclisation was determined to have the same characteristic spectroscopic features as those produced from the minor isomer in case of enones (**130** and **139**). The key feature was the characteristic double-doublet peak at  $\delta = 1.00$  ppm which corresponds to one of two protons next to the carbonyl group in the cyclohexene ring. Therefore, it appears that the stereochemical outcome of the cyclisation reaction of sulfinyl amide substrate **159** was opposite to that produced upon cyclisation of sulfinyl esters **130** and **139**.

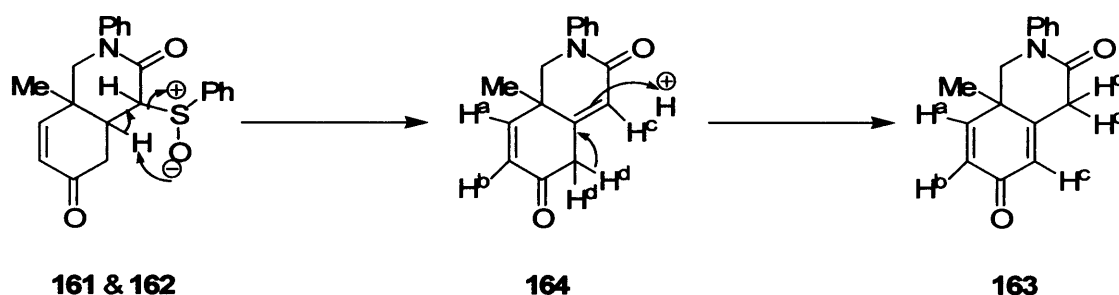
Upon purification of the crude reaction mixture, the major and the minor isomers were isolated as a fairly pure inseparable mixture in 34 % yield. After a second purification the two stereoisomers were still inseparable but another decomposition product **163** was isolated and identified as shown in **Scheme 69**.



**Scheme 69** *Reagents and Conditions:* (i) NaH, THF, r.t, 19 h.

This decomposition product was initially suggested to be intermediate **164** on the basis of mechanistic reasoning. However, examination of spectroscopic data

subsequently confirmed that compound **163** is the correct structure. The  $^1\text{H}$  NMR spectrum indicated the presence of three alkene protons. One of them is a doublet ( $J = 10.0$ ) at  $\delta = 6.71$  ppm which corresponds to  $\text{H}^a$  on the structure below. Another one is doubled-doublet ( $J = 10.0$  and  $1.6$ ) at  $\delta = 6.32$  ppm which corresponds to  $\text{H}^b$  on the structure below. The third one is a broad singlet at  $\delta = 6.17$  ppm. Examination of this peak shows what appears to be a poorly resolved triplet with a small coupling constant. This seems more consistent with  $\text{H}^c$  on structure **163** than with the equivalent hydrogen on structure **164**. The small coupling on  $\text{H}^b$  is presumably due to coupling to  $\text{H}^c$ . The additional coupling on  $\text{H}^c$  is due to coupling to one of the  $\text{H}^d$  hydrogen atoms. It is reasonable that  $\text{H}^c$  might only couple to one of these hydrogen atoms due to the difference in dihedral angle. In structure **164**,  $\text{H}^b$  would presumably appear as a doubled triplet if any long-range coupling (triplet) was observed, although  $\text{H}^c$  could still appear as a triplet, so that distinguishing these structures is not straightforward. All of these data are in favour of structure **163** which formed by the rearrangement of intermediate **164**. Therefore, formation of this decomposition product may be explained by the following sequence of reactions (**Scheme 70**).



**Scheme 70** The proposed mechanism for the formation of the decomposition product **163**

## 2.5. Conclusion

At that point then, we had established that diastereoselective cyclisation reaction of cyclohexa-1,4-diene could be controlled by a chiral sulfoxide group. This is the first time that this has been achieved; however, the level of the stereoselectivity in the above reactions was (2:1) which is acceptable but there is significant room for improvement.

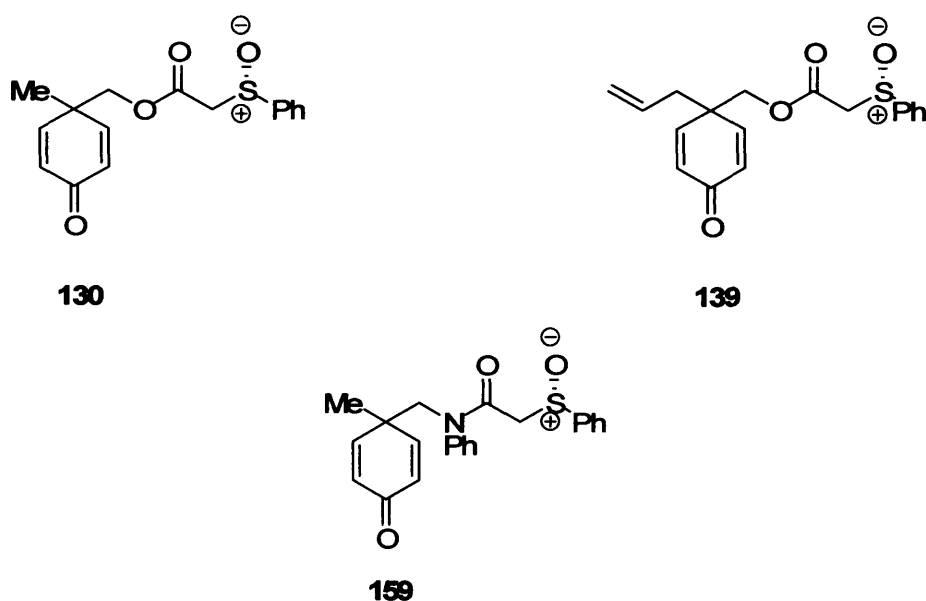
## **Chapter 3**

# **Desymmetrisation Strategies – Further Studies**

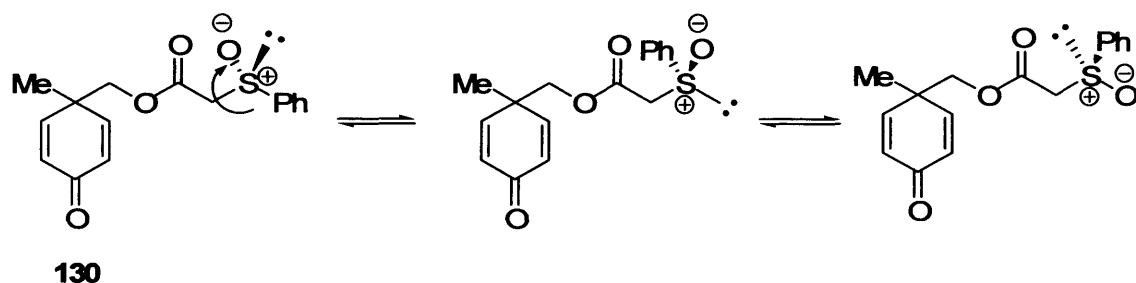
[Through out this chapter, single sulfoxide stereochemistries are indicated by dashes or wedges to indicate the stereogenic centre, but all are racemates. When there is more than one stereogenic centre, the relative stereochemistries proposed are based either on X-ray data and/or mechanistic speculations: in all such cases, the compounds are also racemates].

### 3.1. Introduction

The previous chapter described desymmetrisation strategies of the two diastereotopic double bonds of 1,4-cyclohexadiene derivatives **130**, **139**, and **159** using a chiral sulfoxide group. This reaction featured the stereoselective formation of one quaternary stereogenic centre and two highly crowded vicinal stereogenic centres. The level of the stereoselectivity was acceptable (2:1) but there is significant room for improvement.



One possible reason for the modest stereocontrol is the free rotation of the stereodirecting sulfoxide (**Scheme 71**).

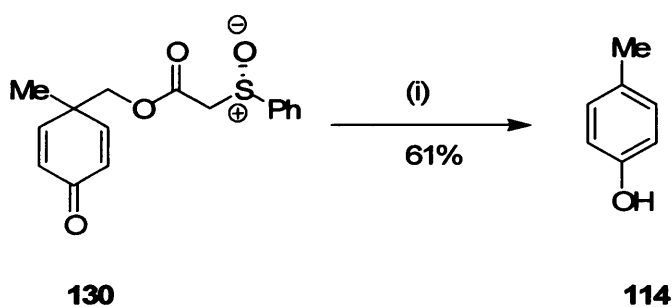


**Scheme 71**

Therefore, the use of divalent metal ions to chelate the sulfoxide oxygen and the ester oxygen, thereby increasing the rigidity of the transition state, may increase the



diastereoselectivity.<sup>44</sup> Toward this approach, zinc bromide was chosen in the first instance. To form the chelate before the addition of potassium *t*-butoxide, cyclohexadienone sulfoxide **130** was treated first with one equivalent of zinc bromide and this mixture was stirred for 45 min. Then two equivalents of potassium *t*-butoxide were added and the stirring was continued at room temperature for 19 hours. Standard work-up of the reaction mixture showed that the starting material was unchanged. Repeating the reaction with one equivalent of zinc bromide and stirring for one hour followed by the addition of a large excess of the potassium *t*-butoxide (10 equiv.) and stirring for 18 hours, unfortunately, resulted in formation of compound **114** as the sole product. This can be attributed to the fact that complexation with zinc bromide increased the electrophilicity of the ester carbonyl as well as increasing the rigidity of the molecule (**Scheme 72**).

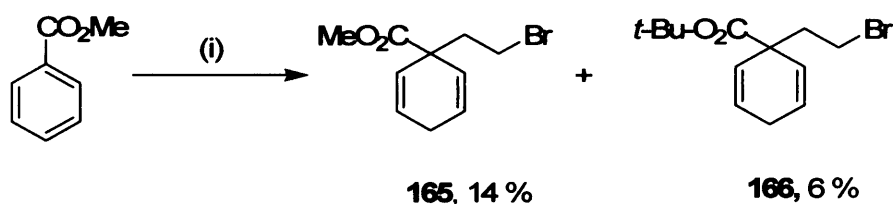


**Scheme 72** Reagents and Conditions: (i) **130**, ZnBr<sub>2</sub>, THF, r.t., 1 h, KO*t*-Bu, 18 h.

Also, the use of isopropylmagnesium chloride as the base, which can deprotonate and chelate at the same time<sup>45</sup>, resulted in formation of a complex mixture. Once again then, the lability of the ester bond was hampering progress. Therefore, we needed to develop a range of substrates which were amenable to cyclisation and were straightforward to prepare. These should not contain an ester linkage (or an amide linkage as it was previously found that this led to problems in the oxidation step discussed).

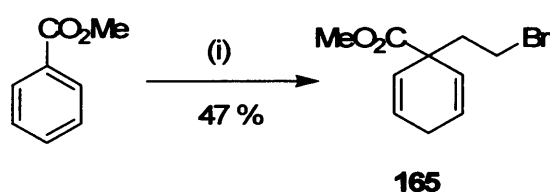
### 3.2. Synthesis of carbon-tether precursors

Towards this goal, precursor **165** was chosen.<sup>33</sup> Birch reduction of methyl benzoate afforded a mixture of compounds **165** and **166**. Compound **166** presumably formed as a result of exchanging the methyl group of the ester at the *ipso* position by a *tertiary* butyl group from the *t*-butanol present in the reaction medium (**Scheme 73**).



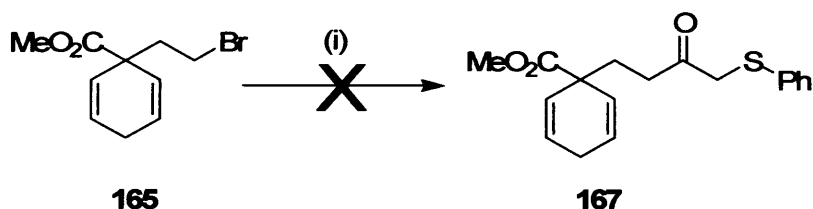
**Scheme 73 Reagents and Conditions:** (i)  $\text{NH}_3(l)$ , Potassium, THF, *t*-butanol, then 1,2-dibromoethane,  $-33\text{ }^\circ\text{C}$ , 1 h, r.t., 18 h.

Therefore, the reaction was repeated by using methanol instead of *t*-butanol as the source of the protons. This resulted in the formation of the desired compound in moderate yield (**Scheme 74**).



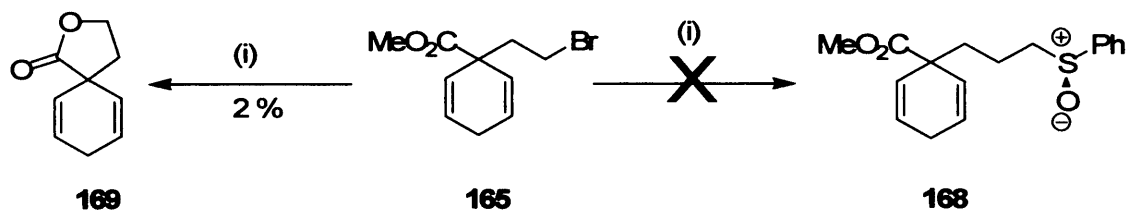
**Scheme 74 Reagents and Conditions:** (i)  $\text{NH}_3(l)$ , Potassium, THF, methanol, then 1,2-dibromoethane,  $-33\text{ }^\circ\text{C}$ , 1 h, r.t., 18 h.

In order to reverse the polarity of the C-Br bond, compound **165** was treated with zinc metal to form an organometallic intermediate<sup>46</sup> that might react with 2-phenylsulfanylacetyl chloride **128** to provide the sulfide precursor **167**. However, this resulted in the starting material was recovered unchanged. Presumably the organometallic compound did not form (**Scheme 75**).



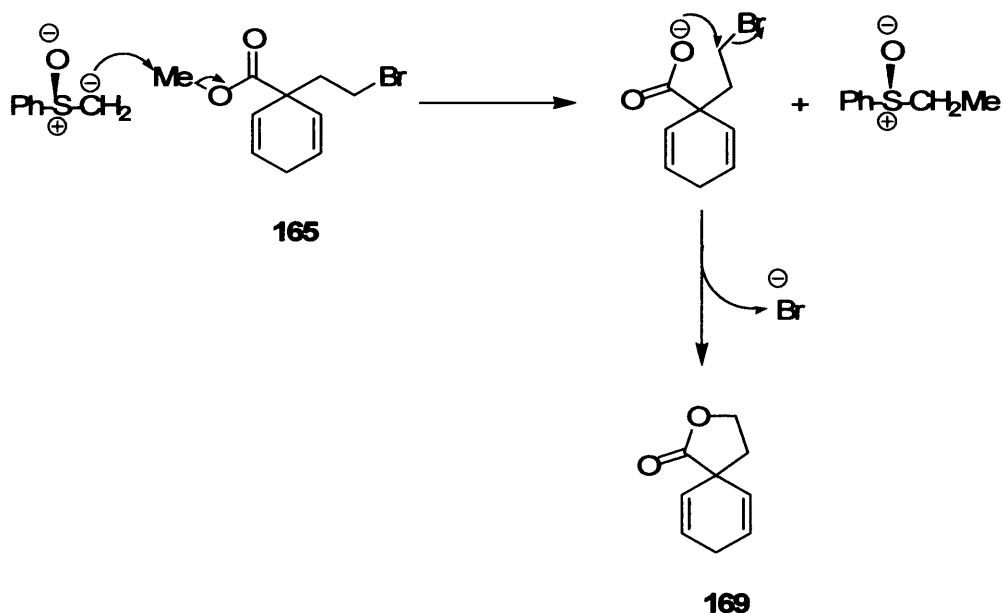
**Scheme 75 Reagents and Conditions:** (i) Zn, 1,2-dibromoethane, TMSCl, THF,  $40\text{ }^\circ\text{C}$ , 2 h, 2-phenylsulfanylacetyl chloride (**128**), r.t., 48 h.

The displacement of the bromide in compound **165** with the methyl phenyl sulfoxide anion was attempted as described in the literature,<sup>47</sup> but this resulted in the formation of compound **169** instead of the desired product **168** (**Scheme 76**).



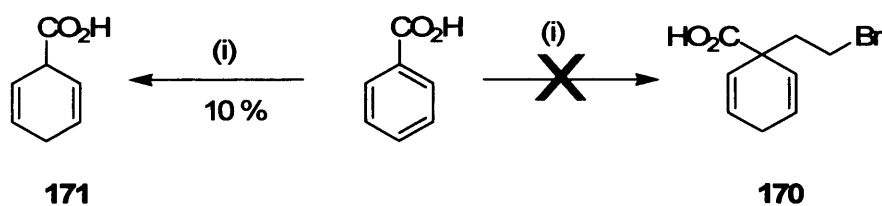
**Scheme 76** Reagents and Conditions: (i)  $\text{PhSOCH}_3$ ,  $n\text{-BuLi}$ , DMPU, THF,  $-78\text{ }^\circ\text{C}$ , 10 min, **165**, r.t., 20 h

Presumably this occurred by attack of the sulfoxide anion onto the methyl ester as shown in **Scheme 77**.



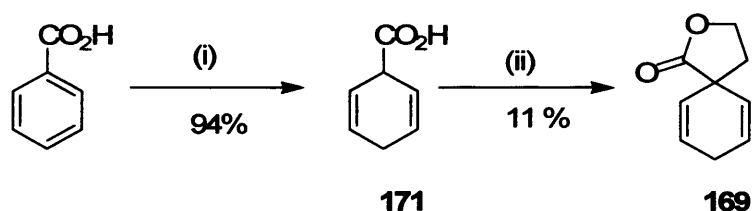
**Scheme 77**

As shown from the previous scheme, the ester side chain needed to form the quaternary centre might not be compatible with the sulfoxide anion. Therefore, Birch reduction and alkylation of benzoic acid with 1,2-dibromoethane was tried next. However, this resulted in formation of compound **171** instead of compound **170** in very low yield (**Scheme 78**).



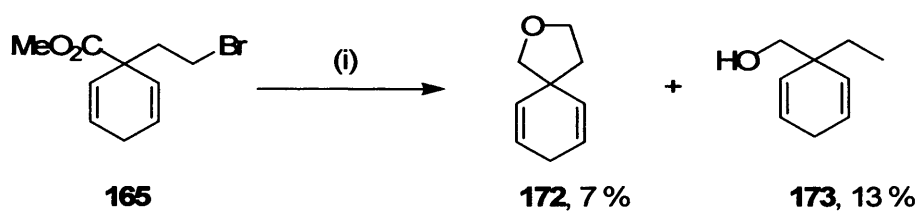
**Scheme 78** *Reagents and Conditions:* (i)  $\text{NH}_3(l)$ , potassium, THF, MeOH, then 1,2-dibromoethane,  $-33\text{ }^\circ\text{C}$ .

Therefore, acid **171** was prepared<sup>48</sup> and deprotonated to give the dianion, which was allowed to react with 1,2-dibromoethane, but this led to formation of compound **169** again (**Scheme 79**).



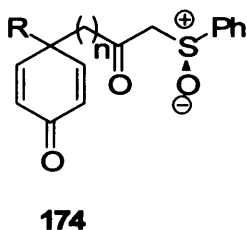
**Scheme 79** *Reagents and Conditions:* (i)  $\text{NH}_3(l)$ , Na, EtOH,  $-33\text{ }^\circ\text{C}$ ; (ii) LDA (2.2 equiv.), THF,  $-78\text{ }^\circ\text{C}$ , **171**, 1 h, 1,2-dibromoethane, r.t., 17 h.

One possible protocol to overcome the problems due to incompatibility of the ester side chain and difficulty in forming acid **170** is to reduce the ester **165** to the alcohol followed by protection. However, upon reduction of compound **165** using  $\text{LiAlH}_4$ , compounds **172** and **173** were formed (**Scheme 80**). This is not entirely surprising.



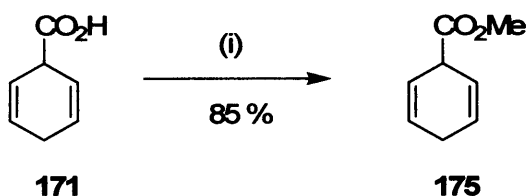
**Scheme 80** *Reagents and Conditions:* (i)  $\text{LiAlH}_4$ , THF, r.t., 1.5 h., NaOH 15 %,  $\text{H}_2\text{O}$ , r.t., 48 h.

Another approach was then designed depending on the formation of a class of compounds having the general structure **174**.



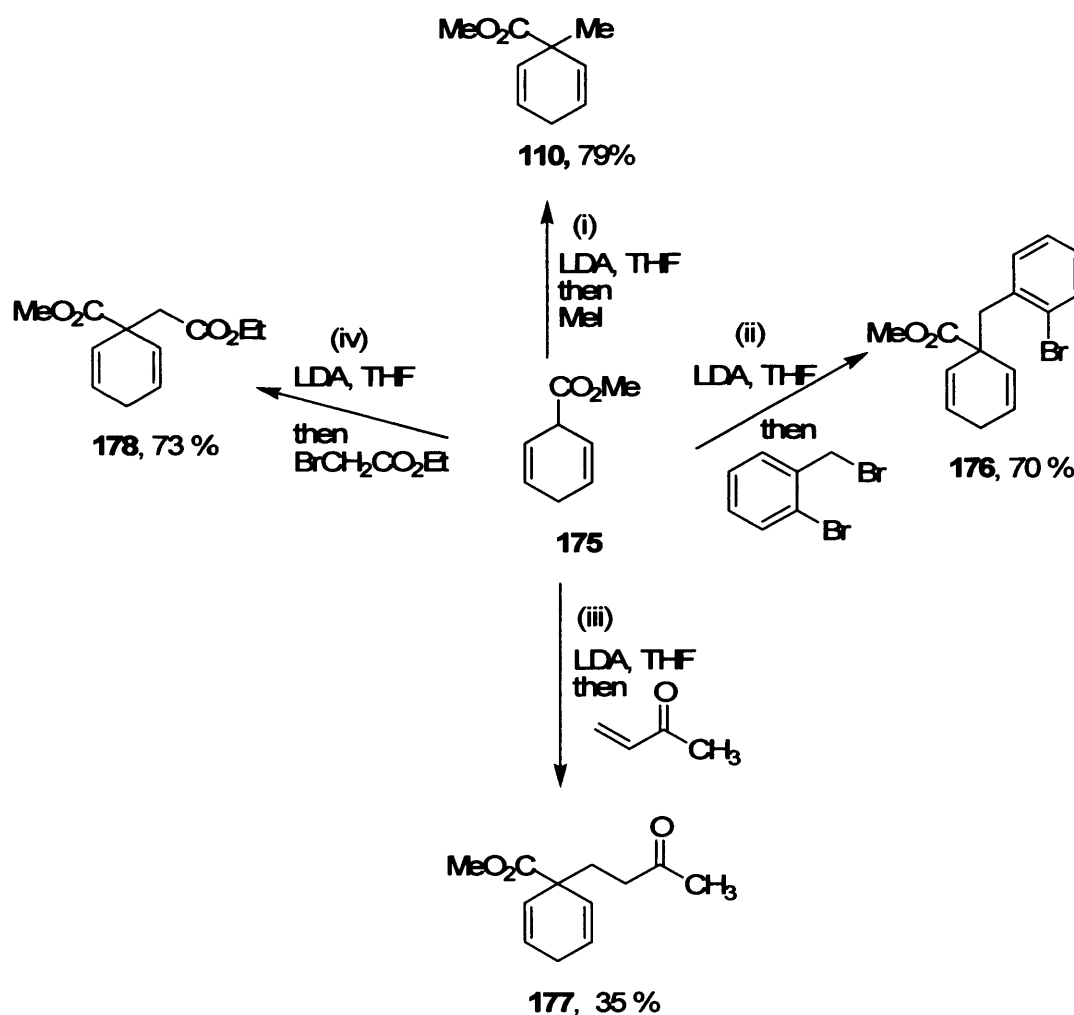
### 3.3. Alkylation of methyl 1,4-dihydrobenzoate

In order to accomplish this goal, a brief survey of the alkylation reactions of compound **175** was carried out. This compound<sup>49</sup> could be readily prepared from compound **171** as shown in **Scheme 81**.



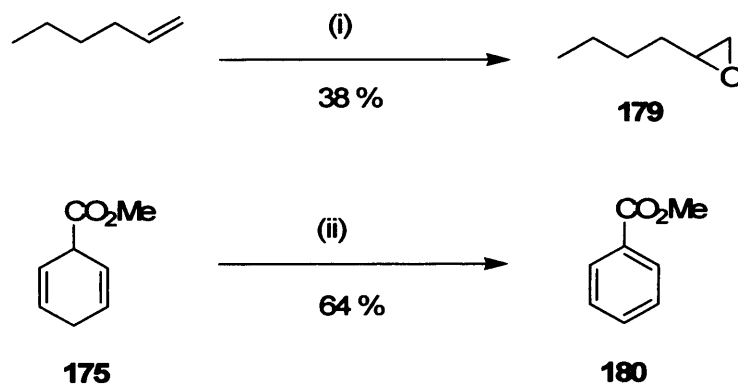
**Scheme 81** *Reagents and Conditions:* (i) MeOH, H<sub>2</sub>SO<sub>4</sub>, r.t., 24 h.

Previously we had generated the anion and alkylated directly during the Birch reduction step. However, this requires an excess of the alkylating agent. While this is acceptable with simple electrophiles such as iodomethane and allyl bromide, a more efficient strategy is needed if we are to use more complex electrophiles to build up the required substrates rapidly. Deprotonation of compound **175** and reactions with a range of electrophiles is shown in **Scheme 82**.



**Scheme 82** Reagents and Conditions: (i) *i*-Pr<sub>2</sub>NH, *n*-BuLi, THF, -78 °C, 30 min, **175**, 30 min., MeI, 1 h, then r.t., 18 h; (ii) *i*-Pr<sub>2</sub>NH, *n*-BuLi, THF, -78 °C, 30 min, **175**, 30 min., 2-bromobenzyl bromide, 1 h, then r.t., 24 h; (iii) *i*-Pr<sub>2</sub>NH, *n*-BuLi, THF, -78 °C, 30 min, **175**, 30 min., methyl vinyl ketone, 1 h, then r.t., 18 h; (iv) *i*-Pr<sub>2</sub>NH, *n*-BuLi, THF, -78 °C, 30 min, **175**, 30 min., ethyl 2-bromoacetate, 1 h, then r.t., 18 h.

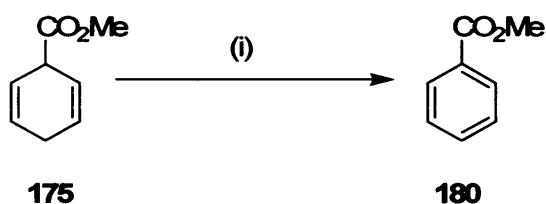
Oxidation of 1-hexene using *m*-chloroperbenzoic acid provided epoxide **179**.<sup>50</sup> This crude epoxide was allowed to react with the anion derived from compound **175** under the standard conditions. However, this resulted in formation of methyl benzoate **180** which can be attributed either to the presence of some *m*-chloroperbenzoic acid left over in the crude reagent or to the fact that this epoxide is not sufficiently reactive which left enough time for the anion to aromatise (**Scheme 83**).



**Scheme 83** *Reagents and Conditions:* (i) 1-Hexene, dry  $\text{CH}_2\text{Cl}_2$ , *m*-CPBA,  $0\text{ }^\circ\text{C}$ , 30 min, then r.t., 18 h; (ii) *i*-Pr<sub>2</sub>NH, *n*-BuLi, THF,  $-78\text{ }^\circ\text{C}$ , 30 min, 175, 30 min., epoxide 179, 1 h, then r.t., 18 h.

The former explanation seems more likely, since subsequent work has shown that the commercially available epoxide reacts well with the anion.<sup>51</sup>

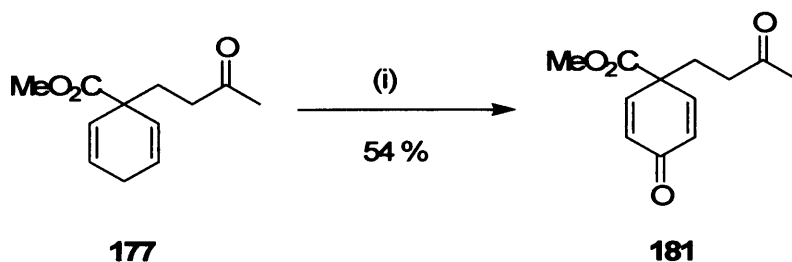
Also when chloroacetone was used as an electrophile under the standard conditions this led to the formation of methyl benzoate again (**Scheme 84**).



**Scheme 84** *Reagents and Conditions:* (i) *i*-Pr<sub>2</sub>NH, *n*-BuLi, THF,  $-78\text{ }^\circ\text{C}$ , 30 min, 175, 30 min., chloroacetone, 1 h, then r.t., 24 h.

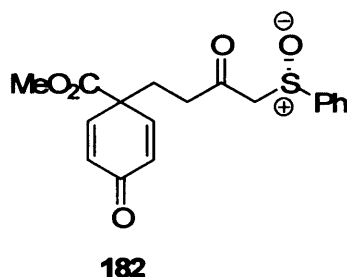
### 3.4. Further studies towards substrate synthesis

The previous alkylation reactions were encouraging, and opened up a number of interesting possibilities for the project. The first of these, as will be discussed in Chapter 4, is the cyclisation of a free-radical derived from compound 176. Also, the formation of compound 177 shows that conjugate addition to unsaturated ketones is feasible with compound 175. Therefore, allylic oxidation of compound 177 under the standard conditions was attempted first prior to the preparation of any precursors using the same mechanism. This oxidation worked well and gave cyclohexadienone 181 as an essentially-pure oil in moderate yield (**Scheme 85**).

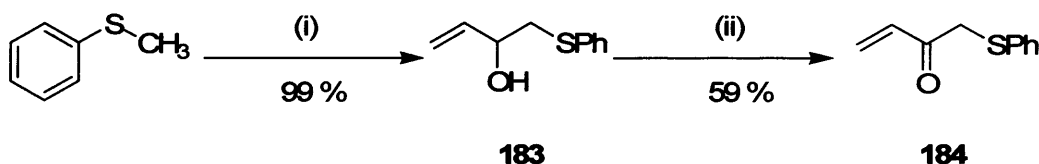


**Scheme 85** *Reagents and Conditions:* (i) 5 - 6 M *t*-BuOOH in decane, PDC, dry benzene, celite, 0 °C, 10 min., then r.t., 18 h.

In order to return to the original objectives of the project, substrate **182** was next considered. This could be prepared from vinyl ketone **184** by analogy with compound **177**.



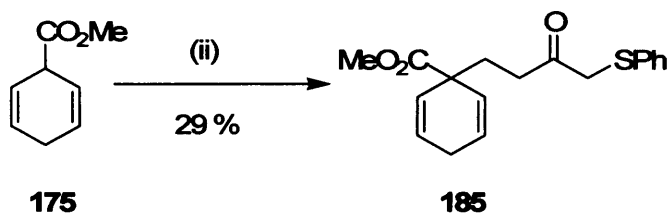
Vinyl ketone **184**<sup>52</sup> was prepared from vinyl alcohol **183**<sup>53</sup> as shown in **Scheme 86**.



**Scheme 86** *Reagents and Conditions:* (i) *n*-BuLi, DABCO, THF, 0 °C, 30 min, r.t., 1 h, then -78 °C, acrolein, r.t., 5 h; (ii) IBX, DMSO, r.t., 6 h.

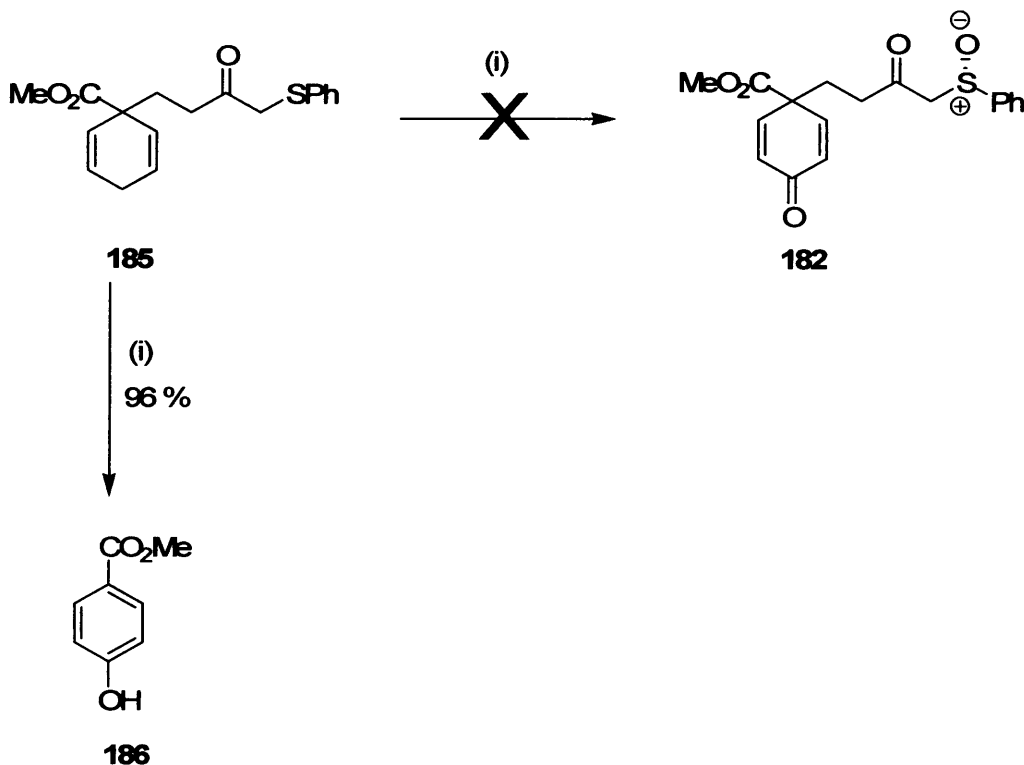
Addition of the anion derived from compound **175** to vinyl ketone **184** worked well and gave compound **185**, albeit in poor yield (**Scheme 87**).





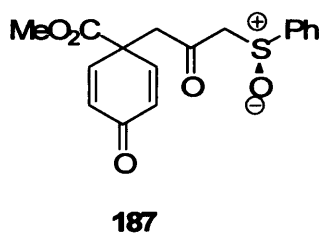
**Scheme 87** *Reagents and Conditions:* (i) LDA, THF, **175**, -78 °C, 30 min, **184**, 1 h, NH<sub>4</sub>Cl.

It was hoped that oxidation of the allylic methylene group and the sulfide would work as before to give the desired compound **182** that will allow us to test our hypothesis that chelation of the sulfoxide and ketone will increase the stereoselectivity of the cyclisation reactions. Unfortunately the allylic oxidation of this compound gave only methyl 4-hydroxybenzoate **186**. This is clearly the result of a combination of stability of the aromatic product and the acidity of hydrogen atoms adjacent to the carbonyl, leading to ready fragmentation (**Scheme 88**).

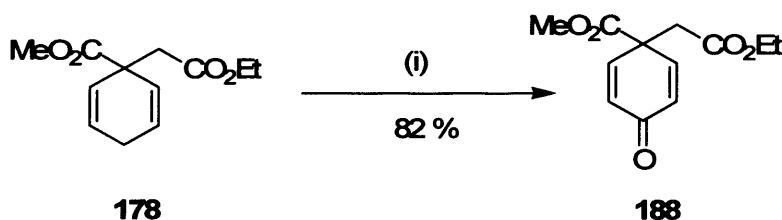


**Scheme 88** *Reagents and Conditions:* (i) 5 - 6 M *t*-BuOOH in decane, PDC, dry benzene, celite, 0 °C, 30 min., then r.t., 15 h.

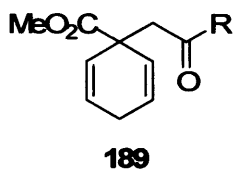
Given this result, compound **187** was the next logical choice with one carbon less than compound **182**.



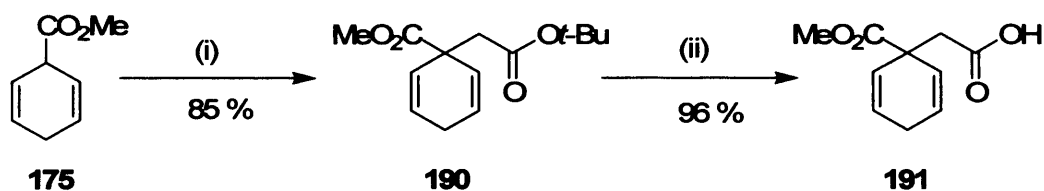
This compound should not undergo ready fragmentation, either itself or any of the obvious precursors, due to the instability of its decomposition compounds compared to those produced from compound **182**. Prior to formation of compound **187**, a test oxidation reaction was carried out using compound **178** as an example of a class of compounds having the general structure **189**; this gave cyclohexadienone **188** under the standard conditions as shown in **Scheme 89**.



**Scheme 89** *Reagents and Conditions:* (i) 5 - 6 M *t*-BuOOH in decane, PDC, dry benzene, celite, 0 °C, 30 min., then r.t., 24 h.

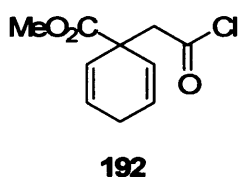


Previously, the scope of alkylation reactions of the anion derived from compound **175** was investigated. We saw an opportunity to use our knowledge of this reaction in the preparation of compound **187**. Deprotonation of compound **175** and reaction with *t*-butyl 2-bromoacetate gave compound **190**. Selective hydrolysis of the tertiary butyl ester side chain of this compound was straightforward, giving acid **191** (**Scheme 90**).<sup>54</sup>

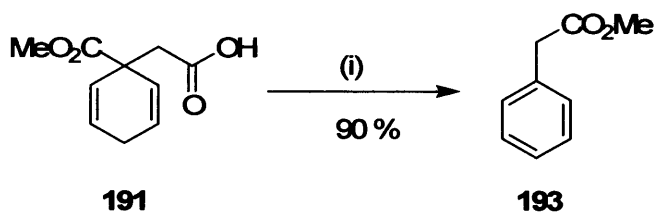


**Scheme 90** *Reagents and Conditions:* (i) *i*-Pr<sub>2</sub>NH, *n*-BuLi, THF, -78 °C, 30 min, **175**, 30 min., *t*-butyl 2-bromo acetate, 1 h, then r.t., 18 h; (ii) TFA, dry CH<sub>2</sub>Cl<sub>2</sub>, r.t., 48 h.

From this point, acid chloride **192** was needed.

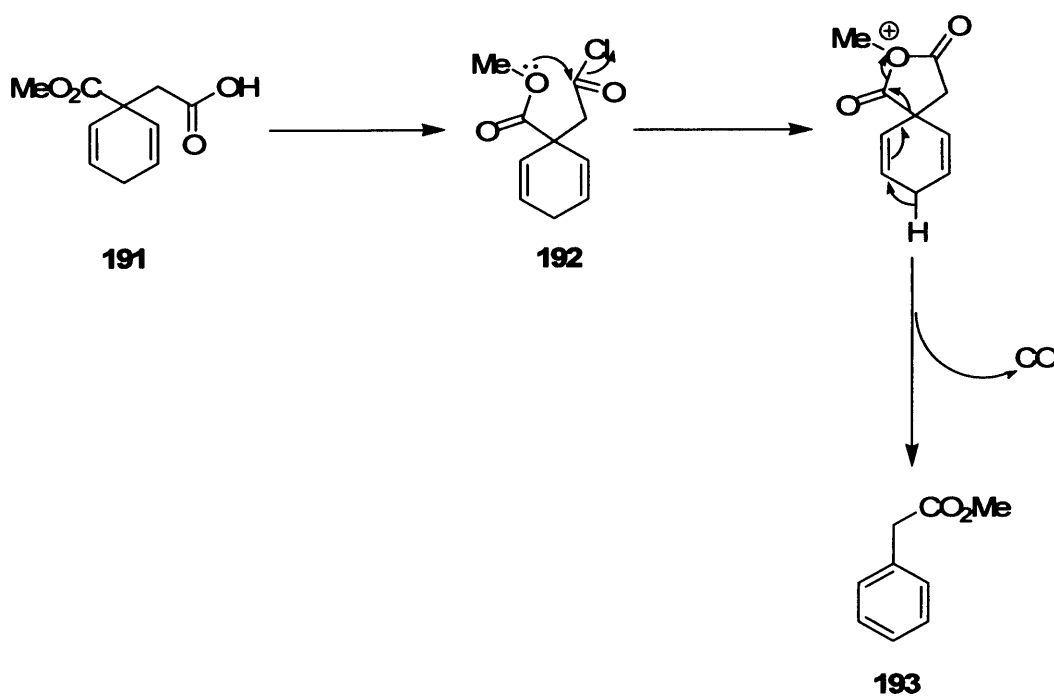


Refluxing acid **191** with excess thionyl chloride for two hours gave an incomplete reaction. Therefore, the reaction was repeated and the reaction mixture was refluxed for a longer time (18 h.). This resulted in evaporation of thionyl chloride and formation of methyl 2-phenylacetate **193** (Scheme 91).



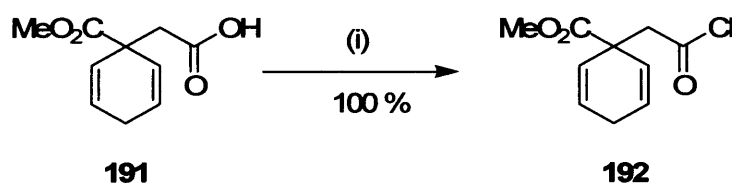
**Scheme 91** *Reagents and Conditions:* (i) SOCl<sub>2</sub>, 18 h, 80 °C.

This is presumably the result of an unexpected rearrangement / decarbonylation as shown in **Scheme 92**.



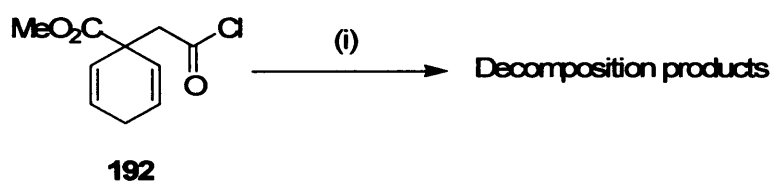
**Scheme 92** Proposed mechanism for formation of decomposition product **193**

Adding thionyl chloride to acid **191** at 0 °C in the presence of triethylamine and DMF gave the impure acid chloride **192**. Because of the sensitivity of this acid chloride, it was difficult to purify it. In the end, the transformation was straightforward by heating acid **191** with thionyl chloride in toluene and few drops of DMF at a temperature not exceeding 60 °C, giving acid chloride **192** as essentially-pure oil in quantitative yield (**Scheme 93**).



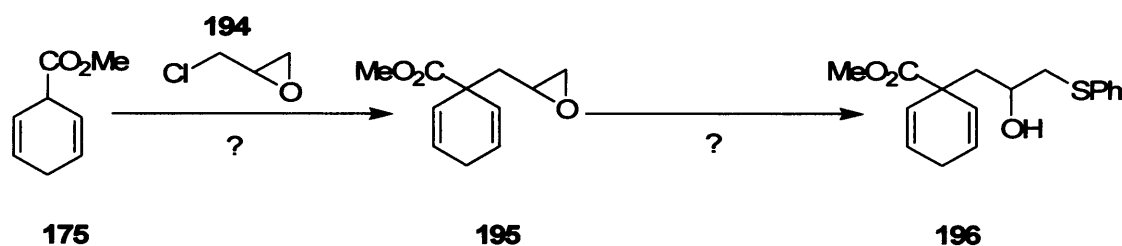
**Scheme 93** *Reagents and Conditions:* (i) SOCl<sub>2</sub>, toluene, DMF, 40 °C, 2 h, 60 °C, 1 h.

The final step was to have been treatment of this acid chloride with the anion derived from thioanisole. Formation of this anion proceeded as before according to the literature method,<sup>53a</sup> followed by addition of the acid chloride **192**. However, this resulted in formation of decomposition products (**Scheme 94**).



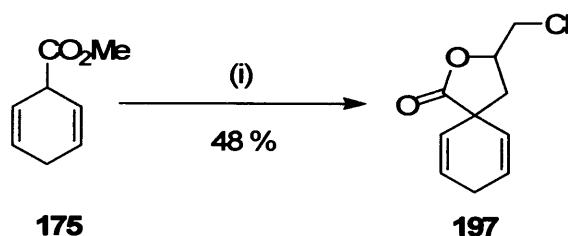
**Scheme 94 Reagents and Conditions:** (i) DABCO, thioanisole, THF, 0 °C, 30 min, *n*-BuLi, r.t., 1 h, then -78 °C, **192**, r.t., 15 h.

Alternative strategies therefore were pursued. We reasoned that the anion derived from **175** should react with epichlorohydrin **194** to give epoxide **195**, irrespective of which carbon atom of epichlorohydrin is initially attacked. This would then be opened with thiophenol<sup>55</sup> to give compound **196**, which only requires oxidation to provide the target compound **187**.



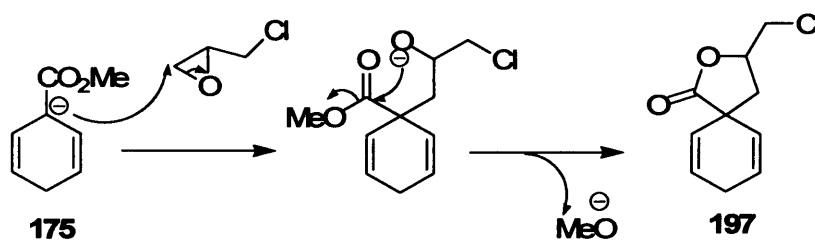
**Scheme 95**

However, when the anion derived from ester **175** was allowed to react with epichlorohydrin, it actually reacted at the epoxide carbon followed by lactonisation to give lactone **197**. This may be due to the fact that the chloride anion is not a very good leaving group (**Scheme 96**).



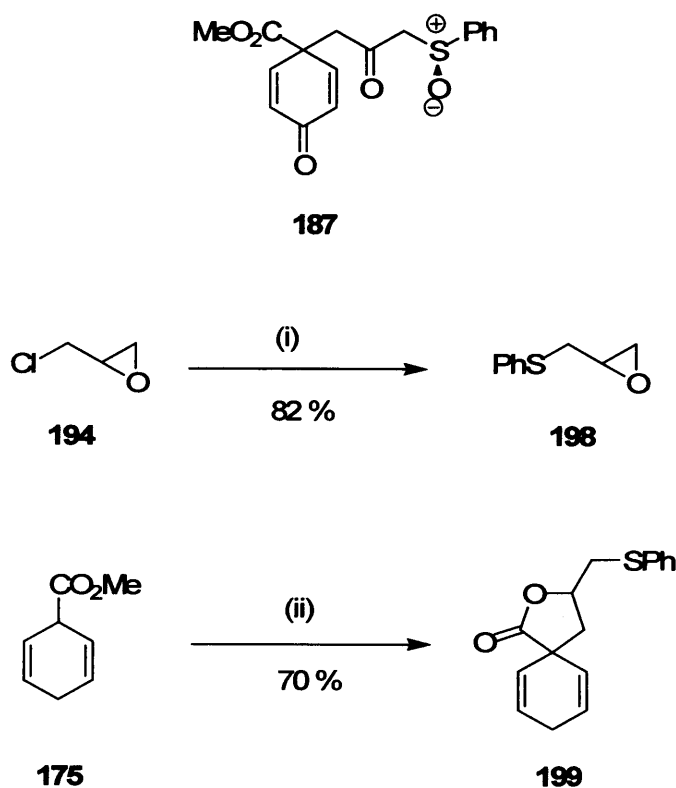
**Scheme 96 Reagents and Conditions:** (i) *i*-Pr<sub>2</sub>NH, *n*-BuLi, THF, -78 °C, 30 min, **175**, 30 min, **194**, -78 °C, 1 h, r.t., 18 h.

The proposed mechanism for the formation of lactone **197** is summarised by the following sequence of reactions (**Scheme 97**).



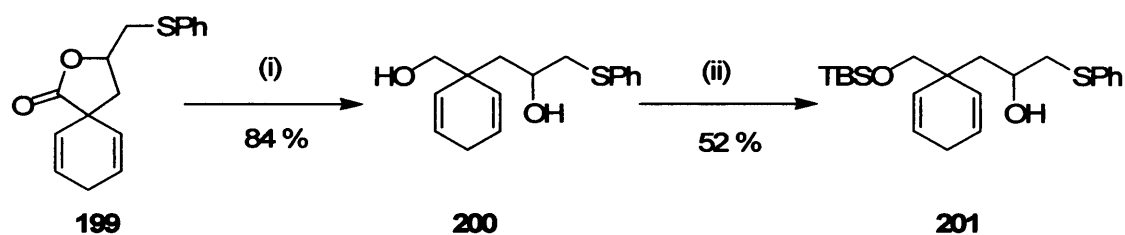
**Scheme 97**

Repeating the reaction using epibromohydrin did not work at all. Only aromatic decomposition products were formed. Therefore, the better approach to the desired compound appeared to be through reduction of the lactone. Based on this result, epoxide **198**<sup>56</sup> was prepared and used to prepare lactone **199** in the same way (**Scheme 98**). This compound contains all carbon and heteroatom functionality required for compound **187**.



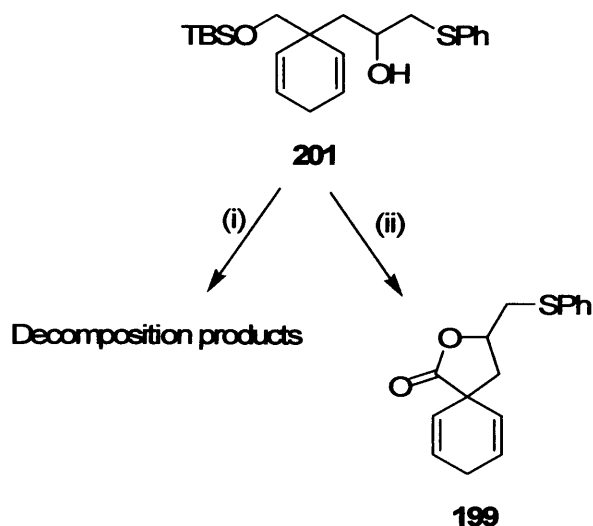
**Scheme 98** *Reagents and Conditions:* (i) Solid NaOH, thiophenol, r.t., 24 h; (ii) *i*-Pr<sub>2</sub>NH, *n*-BuLi, THF, 0 °C, 30 min, -78 °C, **175**, 30 min, then **198**, 1 h, r.t., 16 h.

Reduction of lactone **199** gave diol **200**. Protection of the primary alcohol group as the silyl ether was the next step and this gave alcohol **201** (Scheme 99).



**Scheme 99 Reagents and Conditions:** (i) LiAlH<sub>4</sub>, dry THF, r.t., 18 h., 15 % NaOH, H<sub>2</sub>O; (ii) TBDMSCl, Et<sub>3</sub>N, DMAP, dry CH<sub>2</sub>Cl<sub>2</sub>, r.t., 66 h.

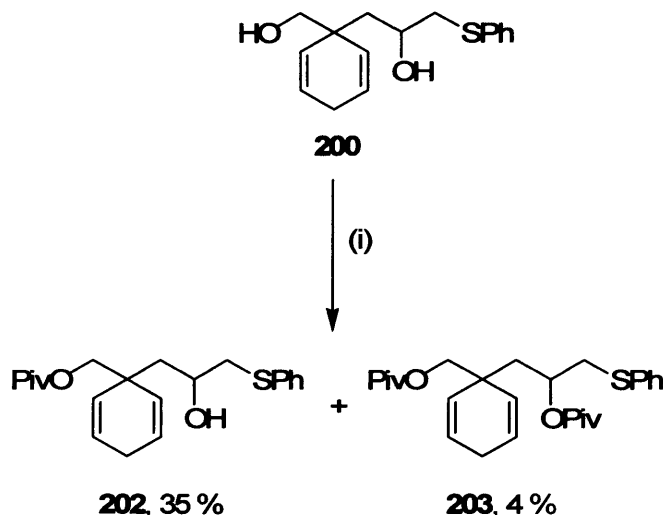
Oxidation under the standard conditions was carried out in the expectation that it would oxidise the sulfide and the allylic methylene group in a single step then oxidation of the secondary alcohol group will follow. However, in this case, only the lactone **199** was formed, presumably by hydrolysis of the silyl ether and selective oxidation of the primary alcohol. Based on this result, it seemed better to try to oxidise each functional group in compound **201** individually. Oxidation of the secondary alcohol group was attempted using DMSO / acetic anhydride,<sup>56</sup> but this gave unknown decomposition products (Scheme 100).



**Scheme 100 Reagents and Conditions:** (i) 5 - 6 M *t*-BuOOH in decane, 0 °C, PDC, dry benzene, celite, r.t., 20 h; (ii) dry DMSO, dry Ac<sub>2</sub>O, r.t., 24 h.

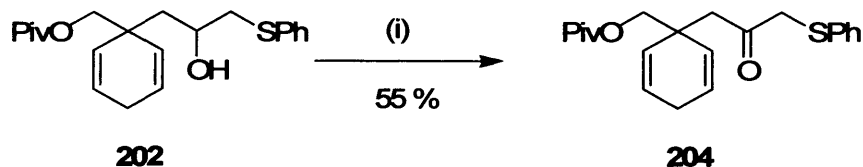
We reasoned that even if the secondary alcohol could be oxidised first, there would still be difficulties with the other oxidation steps in the presence of the silyl ether, so that it was better to modify the approach slightly at this point.

Protection of diol **200** as the pivaloate ester was not as regioselective as the silylation reaction above. Reaction with pivaloyl chloride gave a mixture of mono- and di-pivaloate esters **202** and **203** in 35 % and 4 % yield respectively (**Scheme 101**).



**Scheme 101** *Reagents and Conditions:* (i) PivCl, Et<sub>3</sub>N, DMAP, dry CH<sub>2</sub>Cl<sub>2</sub>, r.t., 15 h.

The mono-pivaloate ester **202** was oxidised at the secondary alcohol position to give ketone **204** (**Scheme 102**).



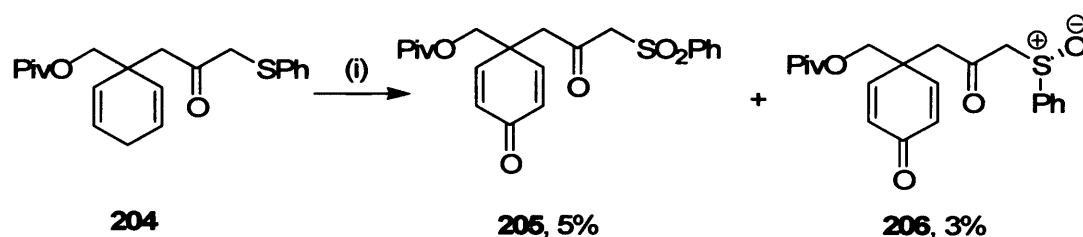
**Scheme 102** *Reagents and Conditions:* (i) IBX, DMSO, r.t., 6.5 h.

Subsequent oxidation of the doubly allylic methylene and sulfide groups in ketone **204** was attempted using a range of different methods which led to different oxidised products. Identification of the obtained products was based on the following criteria: disappearance of the doubly allylic methylene group accompanied by a downfield shift for the alkene protons; the presence of any diastereotopic protons; the splitting



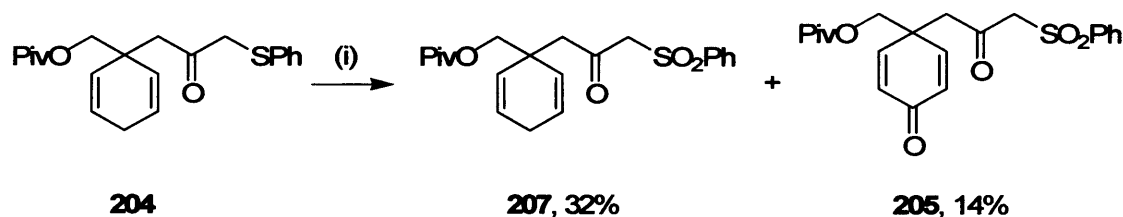
pattern of the aromatic protons which varied from three well-separated peaks to two nearly sharp close peaks to two broad peaks.

Therefore, the use of standard oxidation mixture *tert*-butyl hydrogen peroxide and pyridinium dichromate was deduced to give a mixture of sulfonyl dienone **205** and the desired sulfinyl dienone **206** both in extremely low yield (**Scheme 103**)



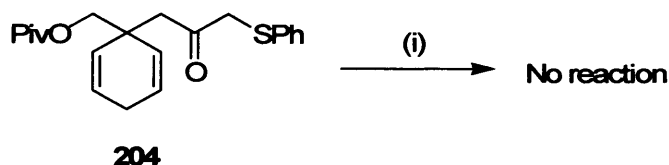
**Scheme 103 Reagents and Conditions:** (i) 5 - 6 M *t*-BuOOH in decane, 0 °C, PDC, celite, dry benzene, r.t., 19 h.

The use of a combination of Jacobsen's catalyst, NMO and *m*-CPBA,<sup>57</sup> yielded a mixture of sulfonyl diene **207** and sulfonyl dienone **205** as shown in **Scheme 104**.



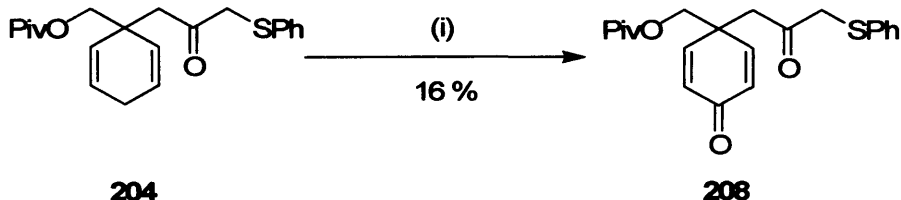
**Scheme 104 Reagents and Conditions:** (i) Jacobsen's catalyst, NMO, dry CH<sub>2</sub>Cl<sub>2</sub>, -30 °C, *m*-CPBA, 24 h.

However, using SeO<sub>2</sub> and *tert*-butyl hydrogen peroxide<sup>58</sup> did not lead to any oxidation and the starting material was recovered unchanged (**Scheme 105**).



**Scheme 105 Reagents and Conditions:** (i) 5 - 6 M *t*-BuOOH in decane, SeO<sub>2</sub>, dry CH<sub>2</sub>Cl<sub>2</sub>, r.t., 30 min, 0 °C, **204**, r.t., 18 h.

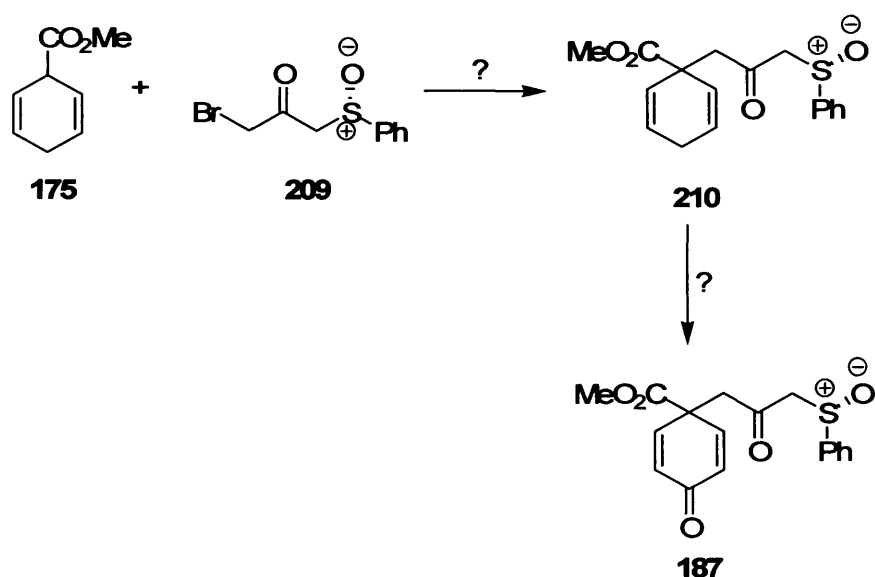
Finally, using pyridinium dichromate in ethanol-free chloroform<sup>42a</sup> led to comparatively clean reaction and sulfanyl dienone **208** was isolated in 16 % yield (**Scheme 106**).



**Scheme 106** *Reagents and Conditions:* (i) PDC, CHCl<sub>3</sub>, 4 Å Molecular sieves, reflux, 9 h.

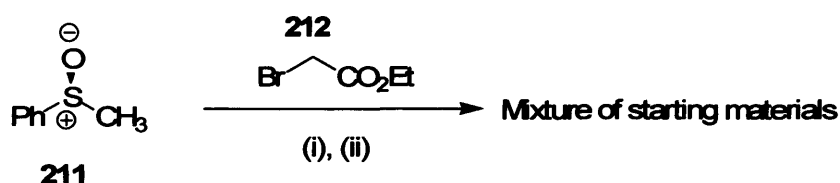
It seemed that even if the oxidation methods could be optimised and directed to give the sulfanyl dienone **208** in a higher yield, the next oxidation will be problematic. All the literature methods used to oxidise the sulfur selectively to sulfoxide include using peracids.<sup>59</sup> The use of peracids, of course, is not compatible with the double bonds and may lead to side epoxidation reactions.

At this point, although these approaches are viable, it would be far better to introduce the entire side chain in compound **175** at the correct oxidation level in a single step. In this case, reaction of compound **175** with  $\alpha$ -bromo- $\alpha'$ -sulfinyl ketone **209** should give sulfinyl diene **210** which just needs allylic oxidation to give the target **187**.



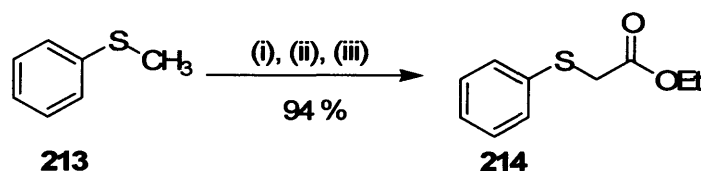
**Scheme 107**

To prepare  $\alpha$ -bromoketone **209** the lithium salt derived from methyl phenyl sulfoxide **211** was formed and then treated with ethyl 2-bromoacetate **212** under the standard conditions. Although, it has been reported that similar sulfoxides were deprotonated and reacted regioselectively with  $\alpha$ -bromo ester substrates to give  $\alpha$ -halo- $\alpha'$ -sulfinyl ketones,<sup>60</sup> this reaction resulted in a mixture of the starting materials being recovered. The failure of the reaction may be attributed to a combination of stability factors and basic properties of the anion which led to abstraction of the acidic  $\alpha$ -proton of the ester instead of attacking the carboxyl group to give the desired product.



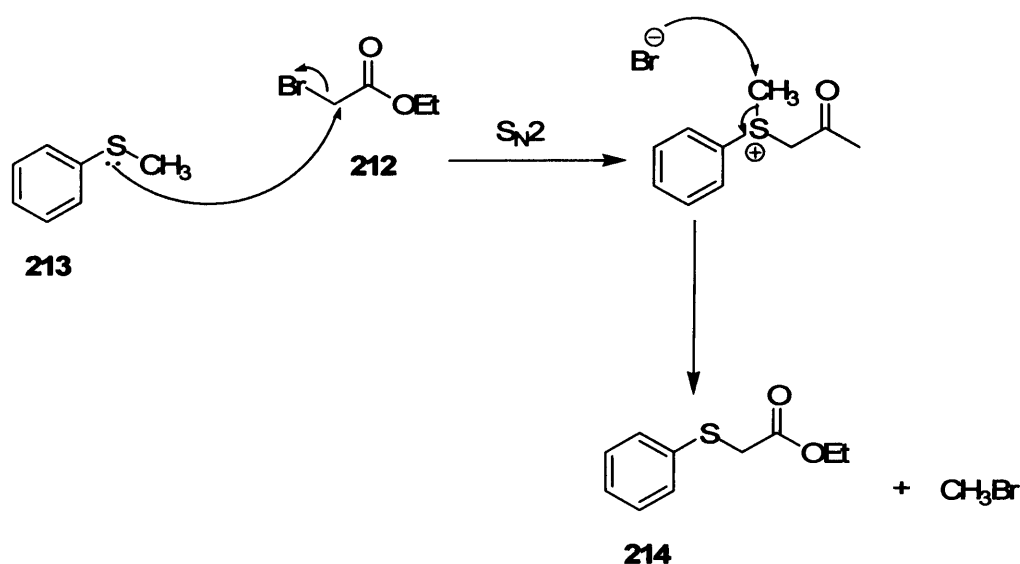
**Scheme 108** *Reagents and Conditions:* (i) *i*-Pr<sub>2</sub>NH, 0 °C, *n*-BuLi, THF, 30 min, bromoester **211**, r.t., 18 h.; (ii) -78 °C, **212**, 1 h., r.t., 18 h.

Therefore, the method was slightly modified by using thioanisole **213**. Deprotonation as before followed by addition of ethyl 2-bromoacetate **212** this time gave  $\beta$ -sulfanyl ester **214**



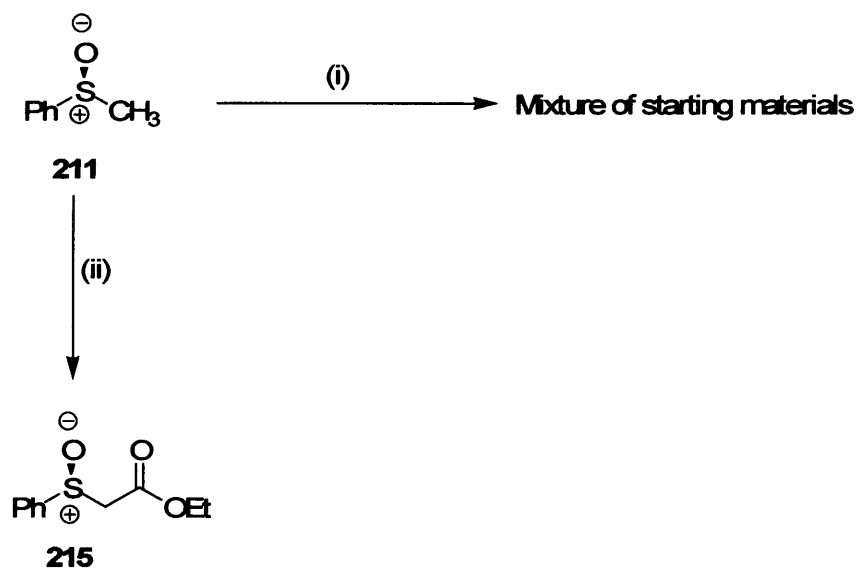
**Scheme 109** *Reagents and Conditions:* (i) Thioanisole (**213**), DABCO, THF, 0 °C, 30 min; (ii) *n*-BuLi, r.t., 1 h, -78 °C; (iii) **212**, then r.t., 15 h.

Formation of compound **214** is presumably due to displacement of the bromine atom by an S<sub>N</sub>2 mechanism using the sulfur lone pair of electrons as the nucleophile as shown in **Scheme 110**.



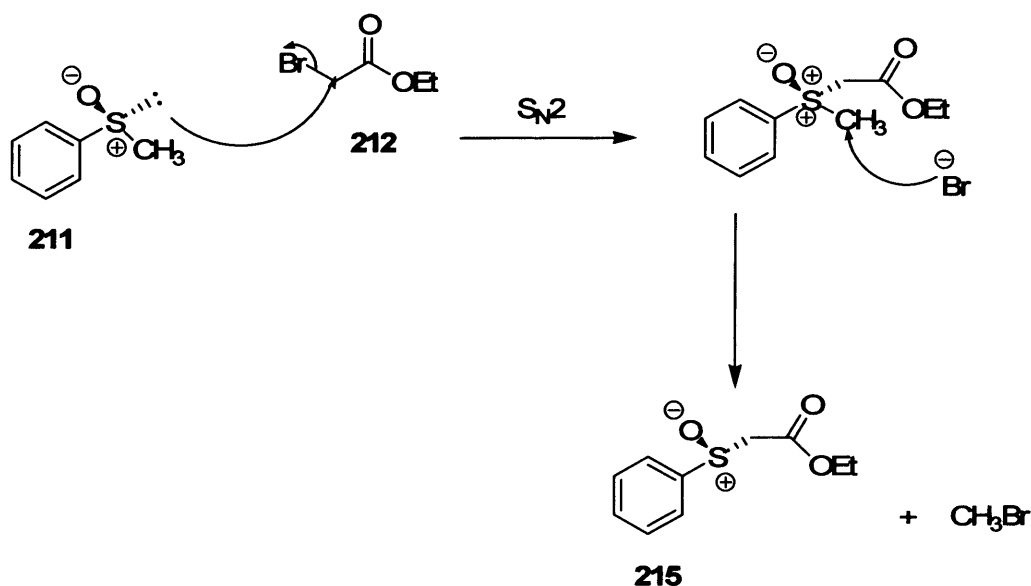
**Scheme 110** The proposed mechanism for the formation of  $\beta$ -sulfanyl ester **214**.

Formation of  $\beta$ -sulfanyl ester **214** was confusing because it indicated that the anion did not form. Therefore, different bases were used to deprotonate methyl phenyl sulfoxide. The use of sodium hydride resulted again in a mixture of starting materials being recovered. The proton NMR spectrum of the crude reaction mixture obtained from using *n*-butyl lithium as the base indicated the presence of some of the two starting materials and formation of some of the undesired  $\beta$ -sulfinyl ester **215** (Scheme 111).



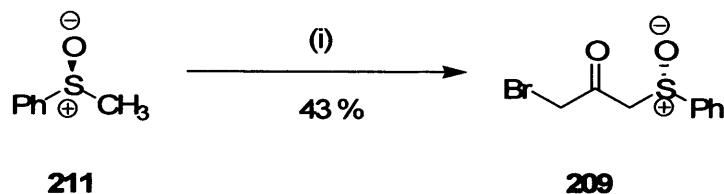
**Scheme 111** *Reagents and Conditions:* (i) NaH dry Et<sub>2</sub>O, 0 °C, **211**, r.t., 19 h, -78 °C, **212**, r.t., 6 h; (ii) **211**, dry Et<sub>2</sub>O, 0 °C, *n*-BuLi, r.t., 19 h, -78 °C, **212**, r.t., 4.5 h.

Compound **215** was formed by the same mechanism that resulted in formation of compound **214** via the displacement of the bromine atom by the sulfur lone pair of electrons instead of the attack by the anion at the carbonyl group to give the desired  $\alpha$ -bromo- $\alpha'$ -sulfinyl ketone **209** as shown in **Scheme 112**.



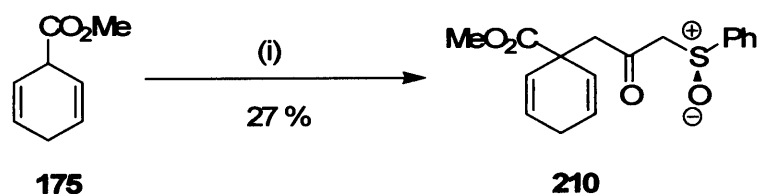
**Scheme 112** The proposed mechanism for the formation of  $\beta$ -sulfinyl ester **215**.

Finally, we were able to adjust the conditions to prepare the desired  $\alpha$ -bromo- $\alpha'$ -sulfinyl ketone **209** in a relatively low yield.<sup>61</sup> It seemed that the problem was mainly in the timing of the addition of the reagents and the molar ratios used. This may be due to combination of instability of the anions and low reactivity of the electrophile used under the reaction conditions (**Scheme 113**).



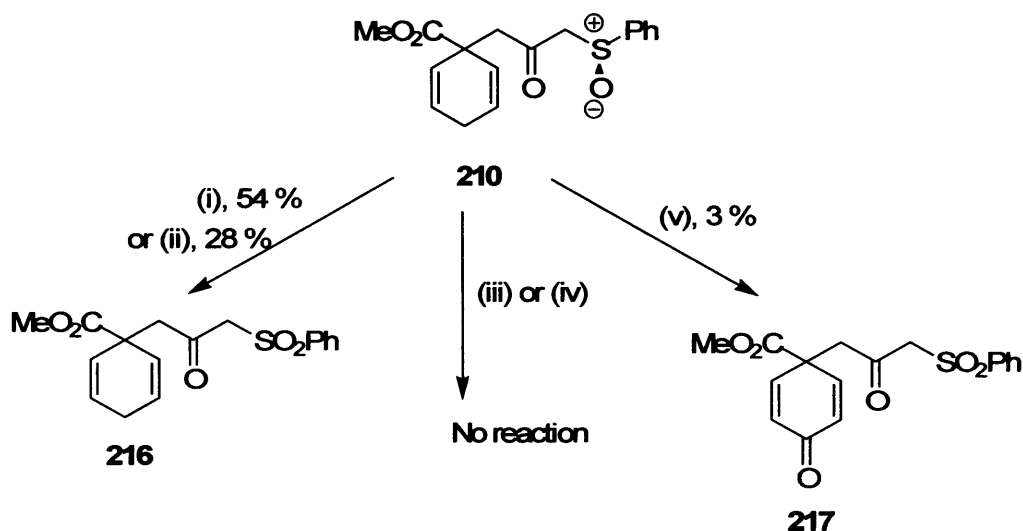
**Scheme 113** *Reagents and Conditions:* (i)  $i$ -Pr<sub>2</sub>NH,  $n$ -BuLi, THF,  $-78$  °C, **211**, 1 h., bromoester **212**, r.t., 1 h.

With  $\alpha$ -bromo- $\alpha'$ -sulfinyl ketone **209** in hand, reaction with the anion derived from compound **175** was performed which gave the requisite sulfinyl cyclohexadiene derivative **210** (**Scheme 114**).



**Scheme 114** *Reagents and Conditions:* (i) *i*-Pr<sub>2</sub>NH, r.t., *n*-BuLi, THF, 30 min., -78 °C, **175**, 1 h., **209**, 1 h.

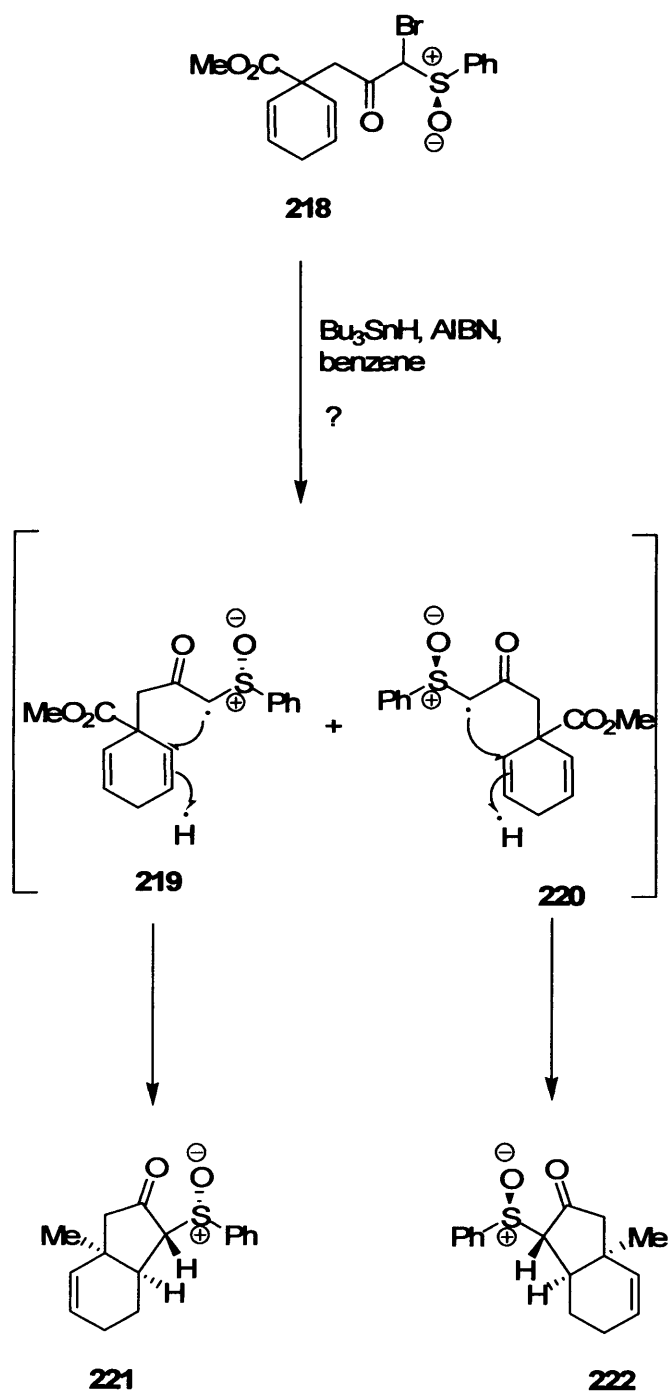
Allylic oxidation of compound **210** was attempted next and again it was problematic. None of the desired sulfinyl cyclohexadienone **187** was formed when a range of oxidising agents were used (**Scheme 115**).



**Scheme 115** *Reagents and Conditions:* (i) **210**, Jacobsen's catalyst, NMO, dry CH<sub>2</sub>Cl<sub>2</sub>, r.t., -30 °C, *m*-CPBA, 24 h; (ii) **210**, PDC, dry CHCl<sub>3</sub>, 4 Å Molecular sieves, reflux 5 h; (iii) CrO<sub>3</sub>, DMP, dry CH<sub>2</sub>Cl<sub>2</sub>, -20 °C, **210**, 15 h; (iv) 5 - 6 M *t*-BuOOH in decane, SeO<sub>2</sub>, dry CH<sub>2</sub>Cl<sub>2</sub>, r.t., 30 min, 0 °C, **210**, r.t., 18 h; (v) **210**, dry benzene, celite, 5 - 6 M *t*-BuOOH in decane, 0 °C, PDC, 1 h., r.t., 15 h.

One possible plan to overcome the problems of the oxidation is to form substrate **218**. In this case the cyclisation would be carried out *via* a free radical mechanism. Due to the free rotation of the sulfoxide side chain there will be two possible conformations for the radical intermediate (structures **219** and **220**). Recognising that the cyclisation would proceed under the influence of the chiral sulfoxide, this may

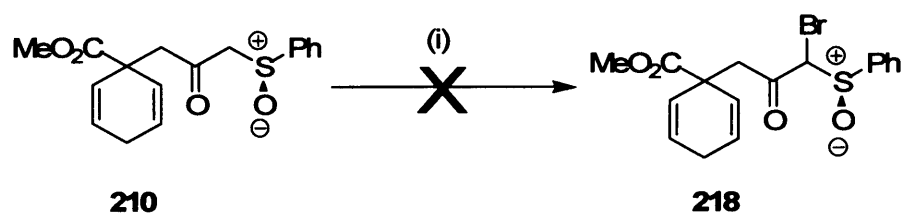
result in one of the two expected diastereoisomers **221** and **222** being favoured over the other (**Scheme 116**).



**Scheme 116**

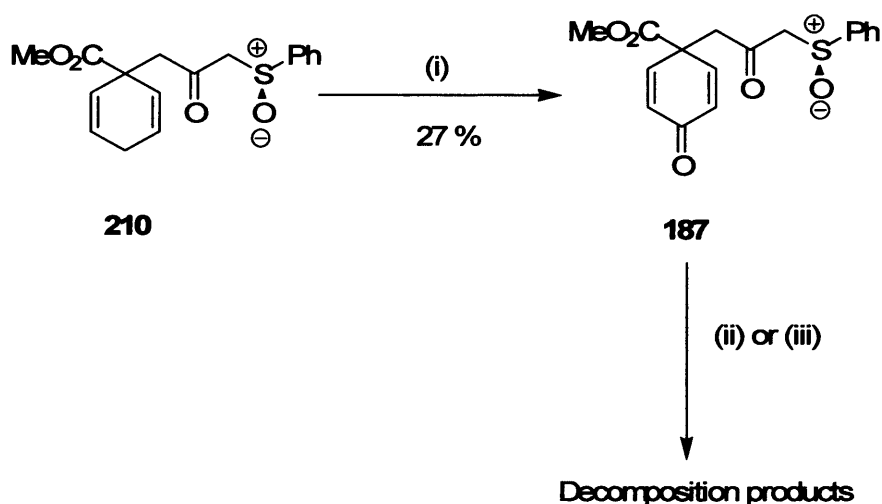
It was thought that compound **218** could be prepared through insertion of a bromine atom in the position  $\alpha$ - to the sulfoxide group in compound **210**. However, upon carrying out the reaction using NBS as the source of bromine, this resulted in the

formation of a complex mixture. Since compound **210** is highly functionalised, perhaps it was optimistic to hope for a clean reaction (**Scheme 117**).



**Scheme 117** *Reagents and Conditions:* (i) **210**, acetone, 0 °C, NBS, 1.5 h.

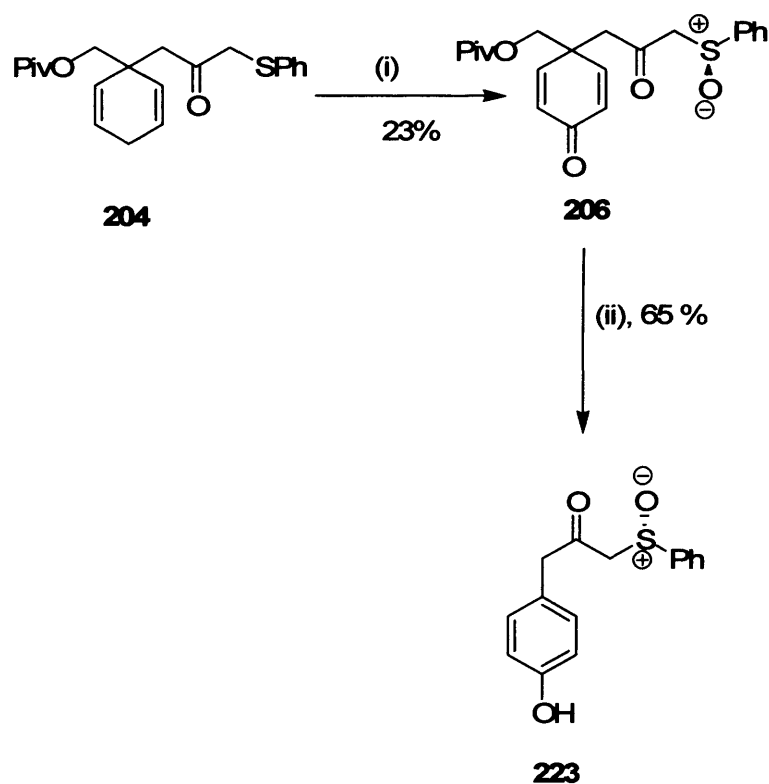
Based on the previous results attempts to accomplish allylic oxidation of compound **210** were resumed. The use of a mixture of pyridinium dichromate and 70 % *tert*-butyl hydrogen peroxide in water at -20 °C<sup>34</sup> worked well and gave the desired sulfinyl dienone **187** in moderate yield. Cyclisation of compound **187** using different bases unexpectedly resulted in the formation of decomposition products (**Scheme 118**).



**Scheme 118** *Reagents and Conditions:* (i) **210**, PDC, *t*-BuOOH 70 % in H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, r.t., -20 °C, 48 h.; (ii) *t*-BuOK, dry THF, 0 °C, 3 h, r.t. 17 h; (iii) NaH, dry THF, 0 °C, 1 h, r.t., 17 h.

Using the same oxidation conditions, compound **204** was oxidised to sulfinyl dienone **206**. Attempted cyclisation of this compound was unfortunately unsuccessful and resulted in formation of decomposition product **223** (**Scheme 119**).





**Scheme 119** *Reagents and Conditions:* (i) **204**, PDC, *t*-BuOOH 70 % in H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, r.t., -20 °C, 48 h.; (ii) NaH, dry THF, 0 °C, 1 h, r.t. 17 h.

### 3.5. Conclusion

To summarise, the previous schemes indicated that preparation of cyclohexadienone core having a carbon tether can be feasibly accomplished by reaction of the lithium salt derived from compound **175** with different electrophiles. This is an easy way to form C-C bonds. Among the electrophiles that can be used are alkyl halides, benzyl halides,  $\alpha$ -haloesters, vinyl ketones and epoxides *via* different mechanisms including S<sub>N</sub>2 reactions and conjugate addition reactions (**Scheme 82**, page 70).

Although, there were a lot of unsuccessful oxidation reactions during the course of this part of the work, the performed experiments showed that some protocols can be successfully used to effect allylic oxidation of sensitive cyclohexadiene derivatives. The first of these protocols is the use of PDC in ethanol-free chloroform for no longer than four hours. The second was using a mixture of PDC and *t*-BuOOH in water. Additionally, cyclohexadiene substrates having the carbon tether were found to be relatively unstable compared to those having an oxygen tether which was reflected on their higher tendency for fragmentation to produce more stabilised aromatic products either during the oxidation or the cyclisation steps *via*

$\beta$ -elimination or deformylation along with decarboxylation or under the effect of heat in the case of acid chloride **192** (page 76).

Moreover, this work provided methods for the preparation of useful synthetic intermediates which in combination with the acquired knowledge about the chemistry of cyclohexadienone derivatives might be used in the future to prepare biologically active compounds.

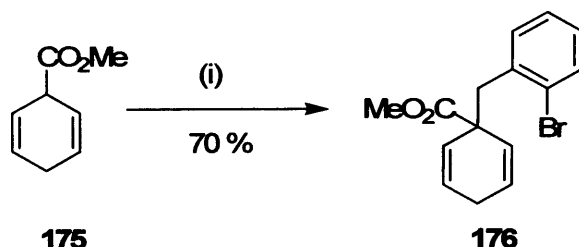
## **Chapter 4**

### **Diastereoselective Free-radical Cyclisation Reactions of Cyclohexa-1,4-dienes**

[Through out this chapter, single enantiomer stereochemistries of the precursors for the free radical cyclisation reactions are indicated by dashes or wedges to indicate the stereogenic centre, but all are racemates. When there is more than one stereogenic centre, the relative stereochemistries proposed are based on NMR studies or on mechanistic speculations: in all such cases, the compounds are also racemates].

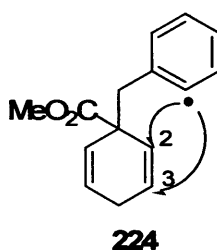
#### 4.1. Cyclisation reactions of aryl radicals

As explained in Chapter 3 the alkylation reaction of the anion derived from ester **175** with 2-bromobenzyl bromide has been successful (**Scheme 120**).

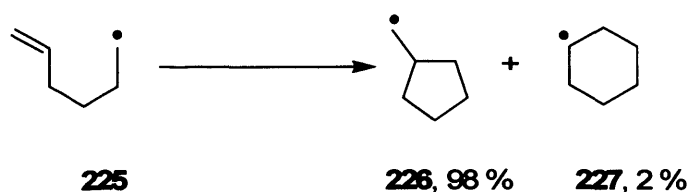


**Scheme 120** Reagents and Conditions: (i) *i*-Pr<sub>2</sub>NH, *n*-BuLi, THF, -78 °C, 30 min, **175**, 30 min., 2-bromobenzyl bromide, 1 h, then r.t., 18 h.

Bearing in mind the original goals of the project - selective attack on one of the two double bonds in a 1,4-cyclohexadiene derivative - substrate **176** is ideal for radical cyclisation onto the cyclohexadiene ring. Although the radical derived from compound **176** is achiral, it would enable us to test the bond forming reactions and the regioselectivity issues in the cyclisation reaction before attempting to prepare chiral analogues. In principle, radical **224** could attack at both the C-2 and/or C-3 positions *via* the allowed 5-*exo*-trig cyclisation and/or 6-*endo*-trig cyclisation modes respectively.

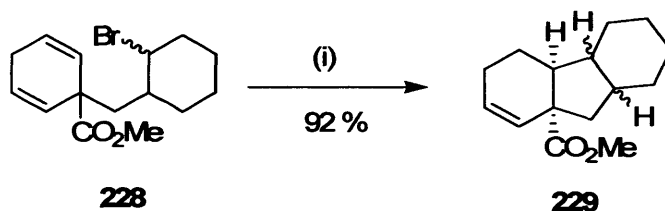


However there are numerous examples in the literature which show that cyclisation of radicals which are four bonds away from the targeted double bond cyclise highly regioselectively in the *exo* mode to afford the cyclopentylmethyl radical. For instance, Beckwith reported that cyclisation of 5-hexen-1-yl radical **225** resulted in the formation of radical **226** predominantly (**Scheme 121**).<sup>62</sup>



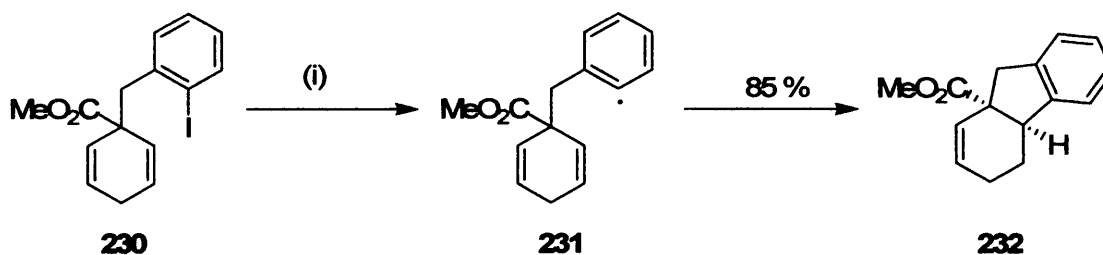
**Scheme 121** 5-*exo*-trig and 6-*endo*-trig radical cyclisation

Then the same author applied this 1,5-radical ring closure methodology to cyclohexadiene derivatives with the aim to synthesize a variety of substituted decalins and hydroindanes with the study of the kinetic, regiochemical, and stereochemical features that are associated with the formation of bi- or tricyclic systems.<sup>63</sup> Using different radical precursors containing the hex-5-en-1-yl system, the reactions proceeded with high regioselectivity. These ring closures resulted exclusively in the product or products of 5-*exo*-cyclisation and no trace of 6-*endo*-cyclisation products. For example treatment of a mixture of epimeric bromides **228** with tributylstannane resulted in the formation of an inseparable mixture of three isomers of the tricyclic product **229** in the ratio of 3.75:1.50:1.00 (G.L.C). They assigned the stereochemistry at the ring junction as a *cis* relationship which was consistent with many other examples examined (**Scheme 122**).



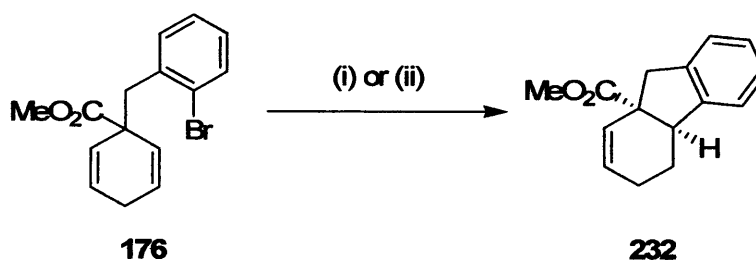
**Scheme 122** *Reagents and Conditions:* (i) **228**, dry benzene, AIBN, Bu<sub>3</sub>SnH, reflux, 80 °C, 12 h.

The same author reported the radical cyclisation reaction of iodide **230** which features the 5-*exo*-trig cyclisation of an aryl radical onto cyclohexadiene ring.<sup>64</sup> This reaction proceeded in regiospecific *exo*-mode *via* aryl radical **231** to afford the tricycle **232** as a sole stereoisomer (**Scheme 123**).



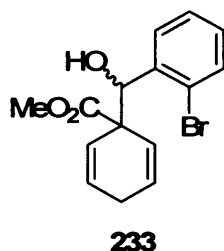
**Scheme 123** *Reagents and Conditions:* (i) **230**, Benzene, AIBN, Bu<sub>3</sub>SnH, heat, 65 °C, 16 h.

In accord with investigating the diastereoselective radical cyclisation reactions of cyclohexa-1,4-diene derivatives, initially compound **176** was treated with tributyltin hydride in the presence of radical initiator AIBN. This resulted exclusively in the formation of the compound **232**, the product of 5-*exo*-cyclisation and no trace of either 6-*endo*-cyclisation product nor the uncyclised reduction product could be detected. This result is in line with Beckwith's observations.<sup>63,64</sup> The low yield obtained in this reaction is due to the difficulty encountered in removal of the tin hydride residues. Therefore another method was tried using tris(trimethylsilyl)silane and triethylborane in the presence of air,<sup>65</sup> but this actually gave a lower yield (**Scheme 124**).

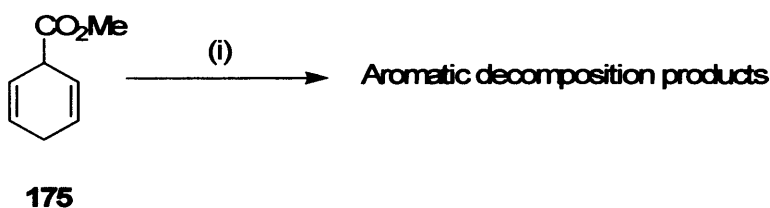


**Scheme 124** *Reagents and Conditions:* (i) Dry benzene, AIBN, Bu<sub>3</sub>SnH, reflux 5 h, 32 %; (ii) Dry benzene, Et<sub>3</sub>B, (TMS)<sub>3</sub>SiH, air, r.t., 5 h, 19 %.

With this result in hand, we next set about preparing chiral cyclohexadiene derivatives to investigate the diastereoselectivity issues. The obvious choice to accomplish this target was to allow the anion derived from ester **175** to react with 2-bromobenzaldehyde to produce radical precursor **233** with the required stereogenic centre that could control the cyclisation of a free-radical.



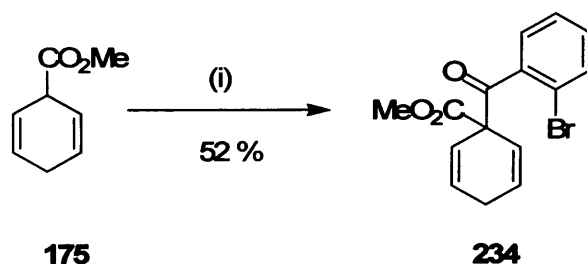
However, deprotonation of ester **175** under the standard conditions followed by the addition of the aldehyde resulted in the formation of aromatic decomposition products (**Scheme 125**).



**Scheme 125 Reagents and Conditions:** (i) *i*-Pr<sub>2</sub>NH, *n*-BuLi, THF, -78 °C, 30 min, **175**, 30 min., 2-bromobenzaldehyde, 1 h, then r.t., 18 h.

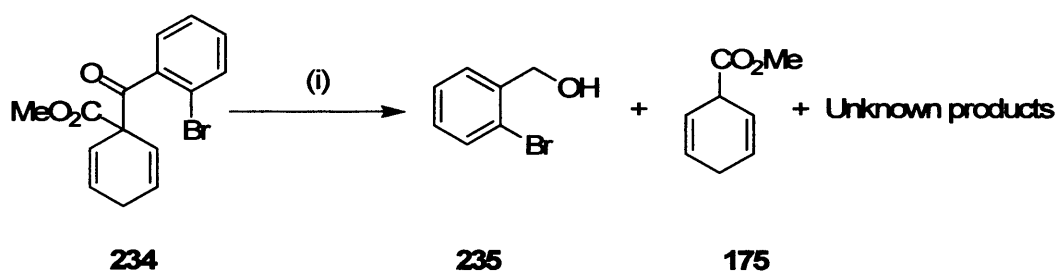
It was not clear why this reaction failed. One possible reason was that the aldehyde is not a very good electrophile, so that nucleophilic addition to the carbonyl group is a slow process and in this case the anion aromatised faster. Therefore, to avoid this possibility, ester **175** was added to a mixture of LDA and 2-bromobenzaldehyde. This again led to the formation of aromatic decomposition products. A further attempt involved formation of the Schlosser base<sup>66</sup> to increase the reactivity of the anion, but this also did not give a better result. Another possibility was that the reaction did work to give the expected alcohol, but this alcohol might be unstable under the reaction conditions, undergoing retro-aldol reaction (as shown below, page 97). To avoid any possibility that this failure is due to reaction conditions or reagents or the anion reactivity, the anion derived from **175** was allowed to react with a (1:1) mixture of 2-bromobenzaldehyde and ethyl 2-bromoacetate. This resulted in a mixture of the product derived from the addition of the anion to ethyl 2-bromoacetate and aromatic decomposition products presumably derived from the addition of the aldehyde. So it was reasonable to find another electrophile. Therefore 2-bromobenzoyl chloride was prepared according to a literature method<sup>67</sup> and

allowed to react with the anion derived from ester **175** under the standard conditions. This resulted in the formation of the keto ester **234** (Scheme 126).



**Scheme 126 Reagents and Conditions:** (i) *i*-Pr<sub>2</sub>NH, *n*-BuLi, THF, -78 °C, 30 min, **175**, 30 min., 2-bromobenzoyl chloride, 1 h, then r.t., 18 h.

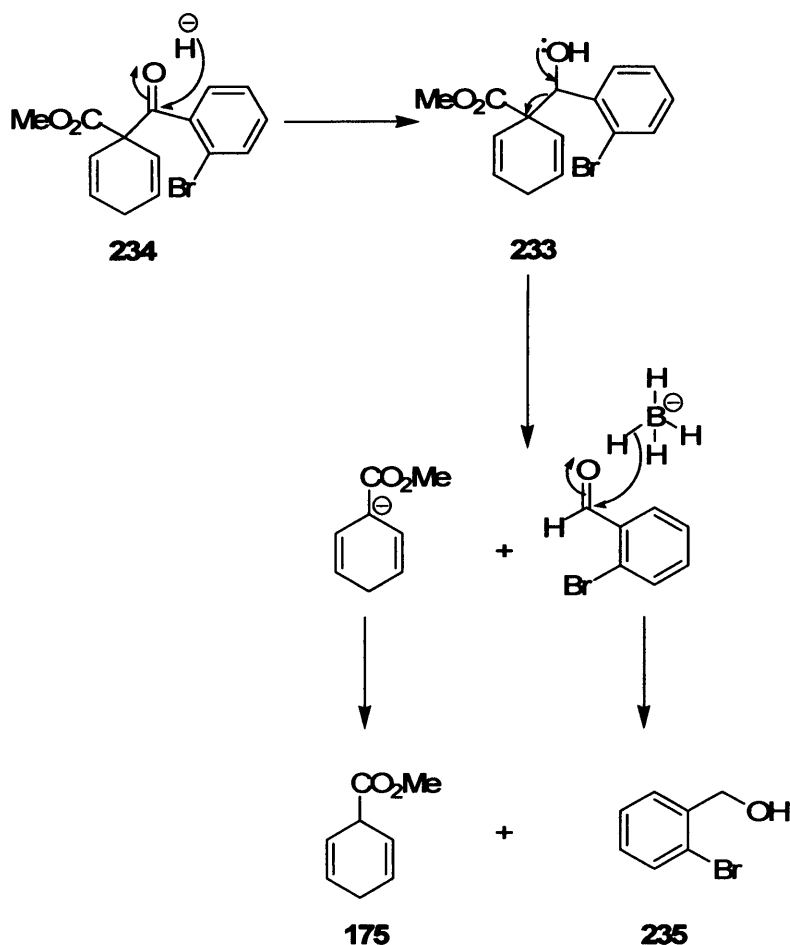
It was expected that selective reduction of the ketone will generate the required chiral radical precursor **233**. However, sodium borohydride reduction of keto ester **234** resulted in a complex mixture of 2-bromobenzyl alcohol **235** and ester **175** and unknown compounds (Scheme 127).



**Scheme 127 Reagents and Conditions:** (i) **234**, MeOH, H<sub>2</sub>O, NaBH<sub>4</sub>, r.t. 15 h

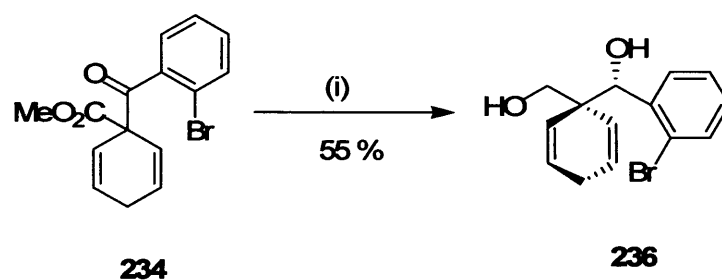
Presumably 2-bromobenzyl alcohol is formed *via* fragmentation of alcohol **233** as shown in Scheme 128.





**Scheme 128** The proposed mechanism for the formation of 2-bromobenzyl alcohol **235**

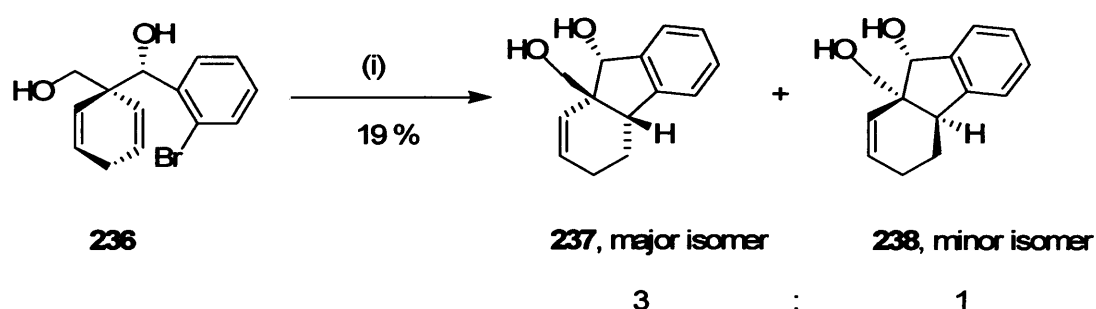
Isolation of 2-bromobenzyl alcohol **235** indicated that alcohol **233** is unstable. This may explain why the reaction between 2-bromobenzaldehyde and the anion derived from ester **175** did not work in the first place. Therefore, complete reduction of both functional groups was attempted using lithium aluminium hydride. This led to the formation of diol **236** having the requisite stereogenic centre.



**Scheme 129** *Reagents and Conditions:* (i)  $\text{LiAlH}_4$ , THF, r.t., 7 h., NaOH 15 %,  $\text{H}_2\text{O}$ , r.t., 24 h

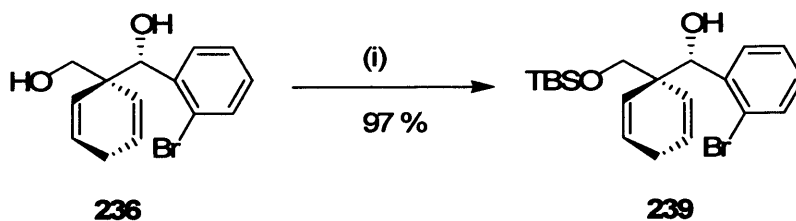
## 4.2. Diastereoselective free-radical cyclisation reactions

Free radical cyclisation of diol **236** under the standard conditions was attempted next. This resulted in the formation of a mixture of two diastereoisomers **237** and **238** (3:1) in 19 % yield. From this mixture, the major isomer, **237**, was isolated in 14 % yield and its structure was fully identified by combination of  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, mass and HRMS spectrometric analysis. The minor isomer was not isolated in a pure form from this reaction but it was obtained from another reaction as will be discussed later. The stereochemistry of both isomers was assigned as shown below based on indirect comparison with related compounds as will be discussed later (**Scheme 130**).



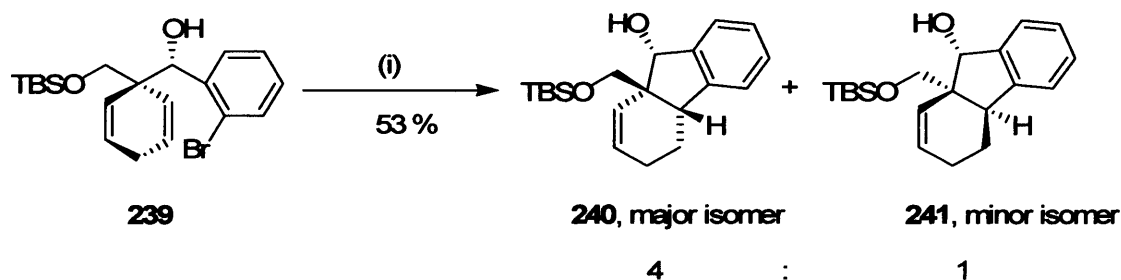
**Scheme 130** *Reagents and Conditions:* (i) **236**, dry benzene, AIBN,  $\text{Bu}_3\text{SnH}$ , reflux 5 h.

This result was extremely encouraging. However, it seemed likely that by introducing protecting groups onto the secondary hydroxyl oxygen, we might enhance the stereocontrol. This is supported by similar work done by Grainger *et al.*<sup>8</sup> where this group showed that the intramolecular addition of a sulfenic acid to 1,4-cyclohexadiene could be controlled by the nature of the protecting group on a chiral alcohol in the connecting chain (Chapter 1, page 10, **Scheme 8**). Therefore, initially the regioselective protection of the primary hydroxyl group in diol **236** as the silyl ether **239** was carried out (**Scheme 131**).



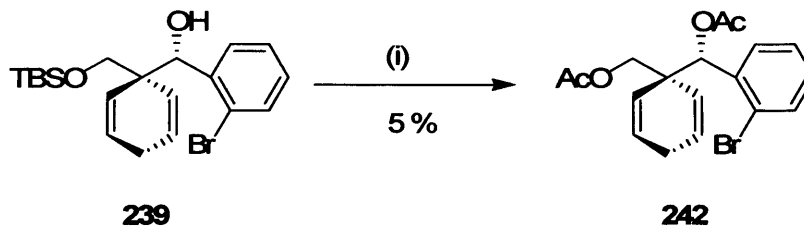
**Scheme 131** *Reagents and Conditions:* (i) **236**, dry CH<sub>2</sub>Cl<sub>2</sub>, TBSCl, Et<sub>3</sub>N, DMAP, r.t., 24 h.

Cyclisation of silyl ether **239** under the standard conditions resulted in a mixture of two diastereoisomers in major:minor ratio of 4:1. The major isomer **240** was isolated pure from this reaction but the minor isomer **241** was not. Assignment of the stereochemistry of both isomers was based on indirect comparison with a related compound as will be discussed later (**Scheme 132**).



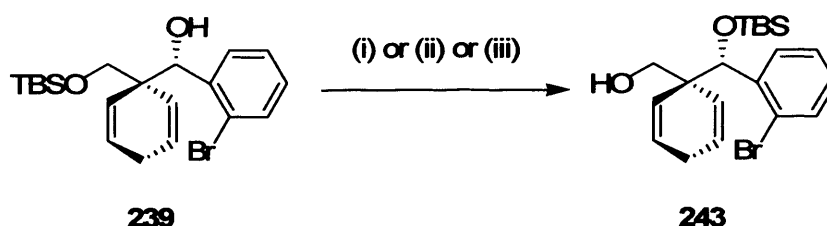
**Scheme 132** *Reagents and Conditions:* (i) **239**, dry benzene, AIBN, Bu<sub>3</sub>SnH, reflux 5 h.

Protection of the secondary hydroxyl group in compound **239** as the acetate was attempted next, but this led to loss of the silyl group and the bis-acetate **242** was isolated in a very low yield (thus it was very difficult to fully characterise this compound) (**Scheme 133**).



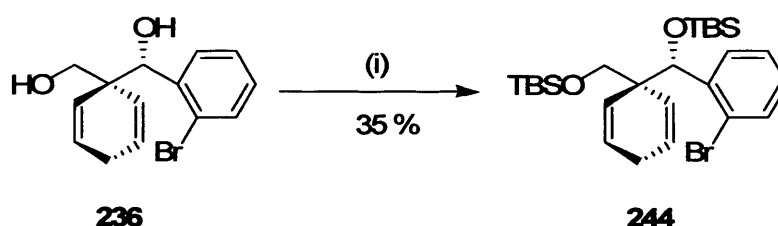
**Scheme 133** *Reagents and Conditions:* (i) **239**, dry CH<sub>2</sub>Cl<sub>2</sub>, Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP, r.t., 24 h.

On the other hand, attempted benzylation did not work under a range of different reaction conditions. Instead, this resulted in the formation of compound **243** in which the silyl group had migrated from the primary to the secondary alcohol position (Scheme 134).



**Scheme 134 Reagents and Conditions:** (i) NaH, dry THF, **239**, PhCH<sub>2</sub>Br, r.t., 24 h, 17 %; (ii) NaH, dry THF, 0 °C, **239**, PhCH<sub>2</sub>Br, KI (catalytic), r.t., 24 h; (iii) NaH, dry THF, **239**, 0 °C, 30 min, PhCH<sub>2</sub>Br, Bu<sub>4</sub>N<sup>+</sup>I (catalytic), r.t., 24 h.

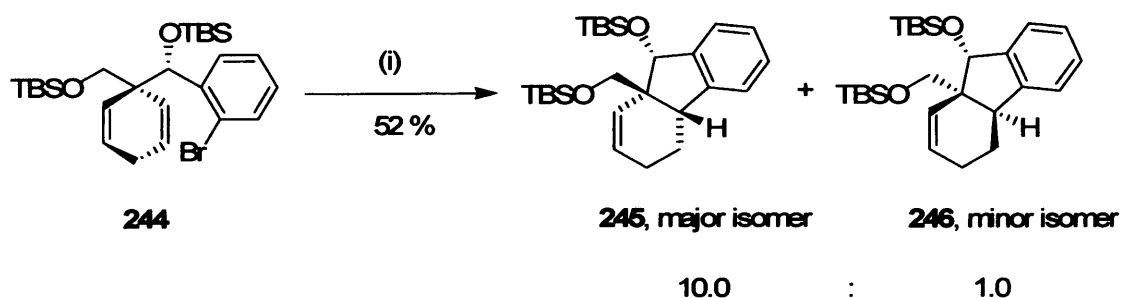
Although compound **243** has very similar spectroscopic features to those of the starting material **239** there were a few differences in the <sup>1</sup>H NMR spectrum which helped to identify the structure. First, all the alkene protons in compound **239** were well separated but in compound **243** three alkene protons were overlapping. Second, the proton at the stereogenic centre was shifted to a more upfield chemical shift value in compound **243**. Third, the two methyl groups attached to the silicon atom became well separated in compound **243** while in the starting material they were overlapping. Therefore, simultaneous protection of both hydroxyl groups was the next choice. Treatment of diol **236** with *tert*-butyldimethylsilyl trifluoromethanesulfonate in the presence of 2,6-lutidine<sup>68</sup> afforded disilyl ether **244** (Scheme 135).



**Scheme 135 Reagents and Conditions:** (i) **236**, dry CH<sub>2</sub>Cl<sub>2</sub>, TBSOTf, 2,6-lutidine, r.t., 20 h.

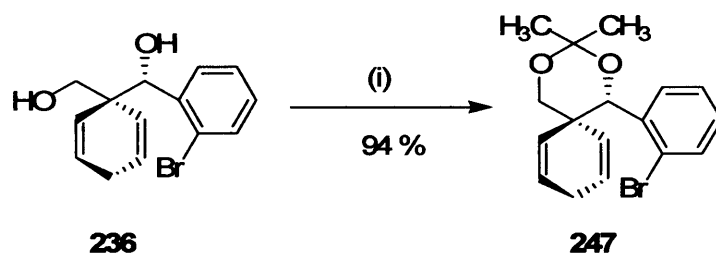
Free radical cyclisation of bis-silyl ether **244** afforded a mixture of two inseparable diastereoisomers, with very good diastereoselectivity (major:minor ratio of 10:1.0)

(**Scheme 136**). The stereochemistry of both the major and the minor isomers was assigned by comparison with related compounds as will be discussed in section 4.3.



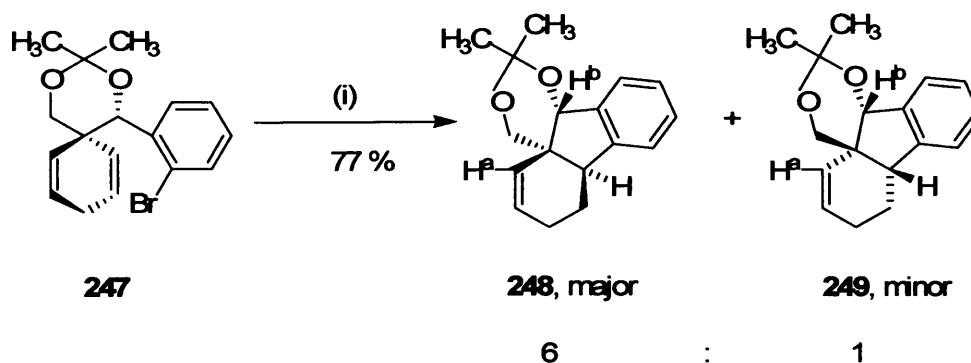
**Scheme 136 Reagents and Conditions:** (i) **244**, dry benzene, AIBN,  $\text{Bu}_3\text{SnH}$ , reflux 5 h.

Finally, tethering the two hydroxyl groups in diol **236** was accomplished by reaction with 2,2-dimethoxypropane which resulted in the formation of acetonide **247** (**Scheme 137**).<sup>69</sup>



**Scheme 137 Reagents and Conditions:** (i) **236**, dry  $\text{Me}_2\text{CO}$ ,  $\text{Me}_2\text{C}(\text{OMe})_2$ , camphorsulfonic acid, reflux, 48 h.

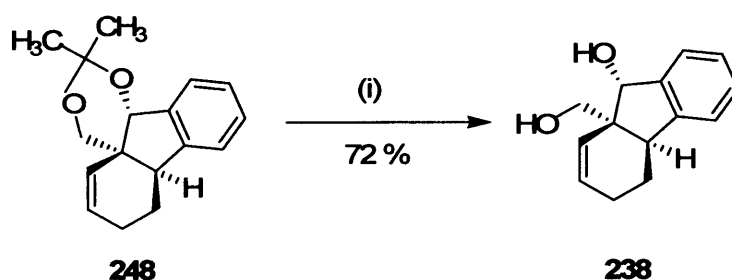
This compound is of particular interest, as tethering the two alcohols reduces the flexibility of the compound considerably which could enhance the diastereoselectivity. Indeed this tethering resulted in a good diastereoselectivity upon carrying out the free-radical cyclisation reaction (major:minor ratio 6:1) (**Scheme 138**).



**Scheme 138** *Reagents and Conditions:* (i) **247**, dry benzene, AIBN, Bu<sub>3</sub>SnH, reflux 5 h.

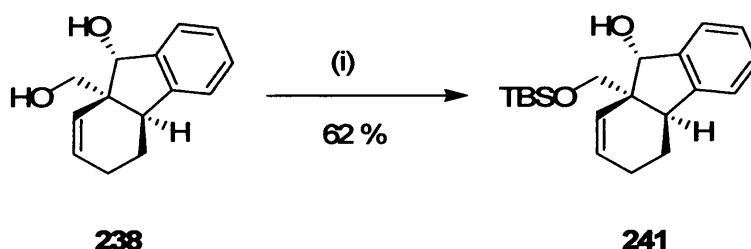
#### 4.3. Assignment of the stereochemistry of the cyclisation products

The stereochemistry of the major isomer **248** was established as shown above based on nOe experiments. Irradiation of the benzylic proton (H<sup>b</sup>,  $\delta$  = 4.74 ppm.) resulted in enhancement of the signals corresponding to the aromatic protons ( $\delta$  = 7.30 - 7.12 ppm.), the alkene proton (H<sup>a</sup>,  $\delta$  = 5.23 ppm.), and one of the two methyl groups ( $\delta$  = 1.55 ppm.). This is a definite proof of the relative stereochemistry shown in structure **248**, since in structure **249**, formed by attack on the other double bond, there will not be any enhancement for the signal corresponding to the alkene proton (H<sup>a</sup>). Although, the stereochemistry of the minor isomer cannot be determined from the crude reaction mixture since it only contains a tiny amount of this isomer, it could be predicted as shown above. This major isomer **248** was used as a reference to establish the stereochemistry of the other obtained products in the previous reactions as indicated before. Hydrolysis of the major isomer **248**<sup>70</sup> would result in the formation of the corresponding tricyclic diol. In this case there are two possibilities; the first is that this resulting tricyclic diol is the major tricyclic diol **237** which was previously obtained by direct free radical cyclisation of its bromide precursor **236**. In this case this product should have the same spectroscopic data as before. The second possibility is that this product is the minor tricyclic diol **238**. Indeed the second possibility was borne out by the experimental results which showed that this product had completely different <sup>1</sup>H and <sup>13</sup>C spectroscopic data from those of tricyclic diol **237**. The NMR data for compound **238** formed from compound **247** correspond with the minor isomer in the crude reaction mixture of the cyclisation of compound **236**. Therefore, the outcome of the hydrolysis of acetonide **248** can be summarised as shown in **Scheme 139**.



**Scheme 139** *Reagents and Conditions:* (i) **248**, AcOH/H<sub>2</sub>O (1:1), r.t., 24 h.

Protecting the primary alcohol in diol **238** afforded the corresponding tricyclic monosilyl product **241** (Scheme 140).



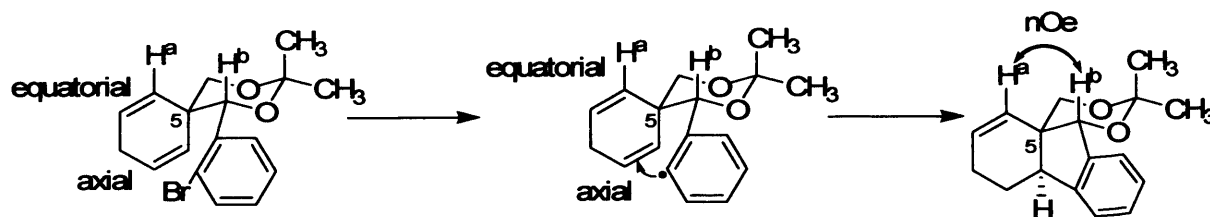
**Scheme 140** *Reagents and Conditions:* (i) **238**, dry CH<sub>2</sub>Cl<sub>2</sub>, TBSCl, Et<sub>3</sub>N, DMAP, r.t., 24 h.

The <sup>1</sup>H and <sup>13</sup>C spectroscopic data of this product were different from those of the major monosilyl tricyclic product **240** which was previously obtained by direct free-radical cyclisation of its bromide precursor **239** (Scheme 132, page 99). But, these data were identical with the minor isomer in the crude reaction of the cyclisation of compound **239**. Therefore, both diastereoisomers of the diol, **237** and **238** can be favoured according to the choice of the protecting group.

#### 4.4. Discussion of the stereochemical outcome of the free radical cyclisation reactions of 1,4-cyclohexadiene derivatives

The stereochemical outcome of the above reactions for all the radical precursors can be rationalised by considering the conformations of the radicals which underwent the 5-*exo*-intramolecular cyclisation step. In case of acetonide **247** the 1,3-dioxane ring would adopt a chair-like conformation where the aryl ring occupies an equatorial position. The cyclohexadiene ring with its two double bonds would be occupying

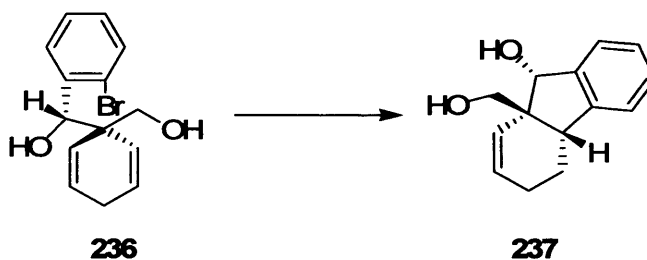
both axial and equatorial positions at C-5 of the dioxane ring. In this case the radical formed would be closer to the axial double bond as shown in **Figure 7**.



**Figure 7**

This leads to the stereochemistry shown. In this representation,  $H^a$  and  $H^b$  are clearly close together explaining the nOe enhancement.

However, in the case of the free diol **236**, monosilyl ether **239** and bis-silyl ether **244** the stereochemical outcome of the two new stereogenic centres is the opposite to that obtained in the case of acetonide **247**. This implies that in the first three cases the radical had attacked selectively a particular double-bond while in the case of acetonide **247** the radical had attacked the other double-bond. This can be explained in terms of the electronic and steric effects since in this case there is no fixed conformation which could be adopted. As shown in **Figure 8** the two hydroxyl groups would try to be as far as possible to avoid the electronic repulsion. From this point the radical is closer to the rear double-bond.



**Figure 8**

The same argument applies to the cyclisation of compounds **239** and **244**.

However the higher level of diastereoselectivity (10:1) observed in the cyclisation of compound **244** compared to both compounds **236** (3:1) and **239** (4:1) could be attributed to the combination of steric effects that greatly enhance the conformational

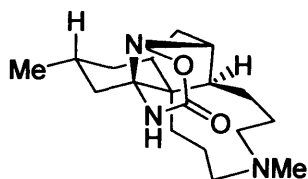


bias toward the rear double-bond in case of compound **244**. In addition to this some possible hydrogen bonding in the case of compounds **236** and **239** may over-ride this preference, giving significant amounts of the diastereomeric product.

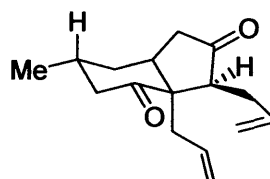
To summarise, a flexible and effective approach to desymmetrise the two diastereotopic double bonds of chiral 1,4-cyclohexadiene derivatives *via* 5-*exo*-trig radical cyclisation has devised. Two new stereogenic centres are created during this process; one of them is a quaternary stereogenic centre. The key element for the control of the stereochemical outcome is the type of the protecting group in the original stereogenic centre.

#### 4.5 Application of radical reactions to lycoposerramine A

As indicated before, the initial inspiration for the chosen methodology was the isolation in 2001 of lycoposerramine A<sup>1</sup> **1** which was extracted from the genus *Lycopodium*. This plant produced the potential therapeutic agent, huperzine A, for the treatment of Alzheimer's disease and many other new alkaloids having biological activities.<sup>71</sup> This complex natural product could be prepared *via* the heavily functionalised carbobicyclic core **2** which would be a key intermediate.

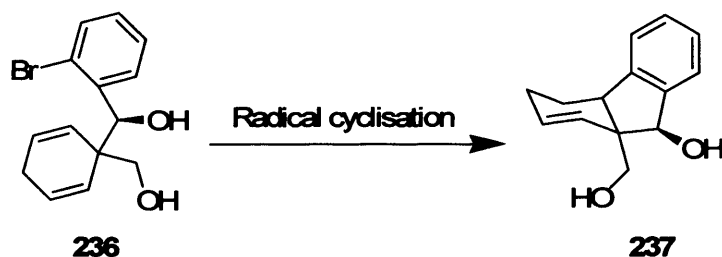


**1**



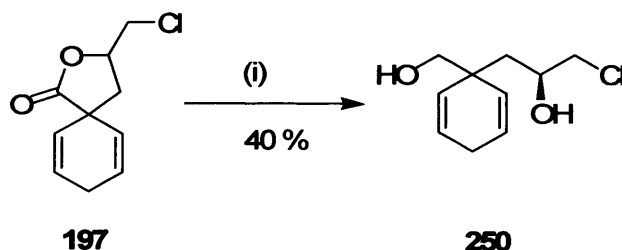
**2**

To demonstrate the synthetic utility of the different approaches described to desymmetrise 1,4-cyclohexadienes, we planned to use radical cyclisation onto cyclohexadiene derivatives to induce the required asymmetry. The model studies we have carried out allowed us to prepare a number of related compounds to structure **2** among them compound **237** which featured the key quaternary stereogenic centre.



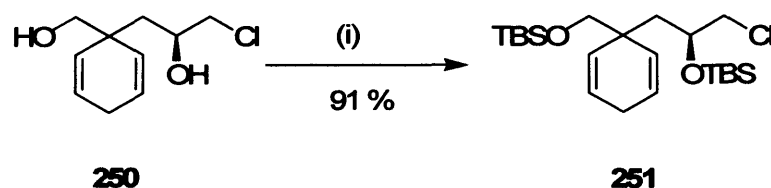
In considering approaches to the key fragment **2** similar compounds to substrate **237** would be suitable for elaboration into compound **2** after some structural modifications. Therefore we addressed the similarities and the differences between compound **237** and this key intermediate **2**. The major differences include the following criteria. Firstly, the natural product is not a benzo-fused compound. Secondly, compound **2** has a ketone and a methyl group on the 6-membered ring. On the other hand the main similarity between the two compounds is that both of them have the fused 5 and 6-membered core in addition to the quaternary stereogenic centre. As the key fragment **2** is synthesised it will need to be elaborated to the 5-6-9 tricyclic carbon skeleton of compound **1**.

At that point it was better to start to prepare substrates having the same basic structure as the key fragment **2** instead of preparing more model substrates. Therefore lactone **197** was chosen for that purpose. Although reduction of this lactone using lithium aluminium hydride resulted in a complex mixture and the desired diol was isolated in poor yield (about 3 %), sodium borohydride reduction<sup>72</sup> delivered diol **250** in a better moderate yield (Scheme 141).



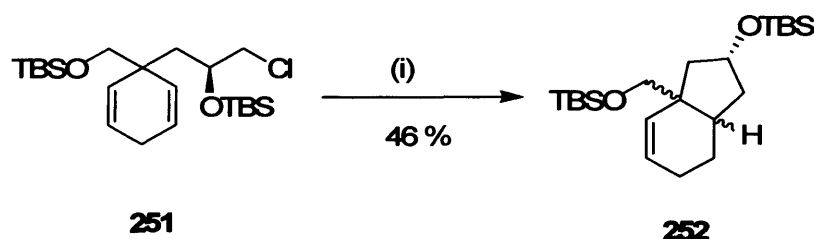
**Scheme 141** *Reagents and Conditions:* (i) **197**, EtOH, NaBH<sub>4</sub>, r.t., 24 h.

Protection of two hydroxyl groups of diol **250** as the TBS ether afforded the bis-silyl ether **251** in 91 % yield (Scheme 142).



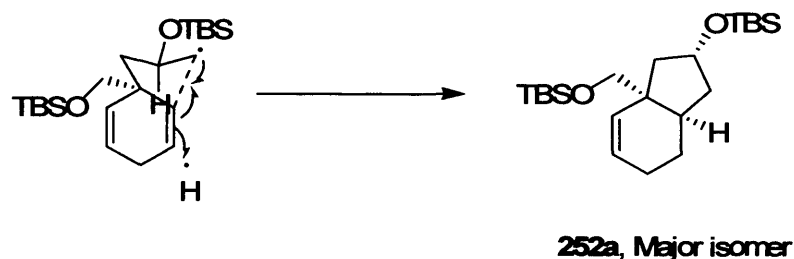
**Scheme 142** *Reagents and Conditions:* (i) **250**, dry  $\text{CH}_2\text{Cl}_2$ , TBSOTf, 2,6-lutidine, r.t., 72 h.

Free-radical cyclisation of bis-silyl ether **251** afforded the desired 5-6-bicyclic core **252** as a mixture of two diastereoisomers in a major:minor ratio of 4.8:1 (**Scheme 143**).



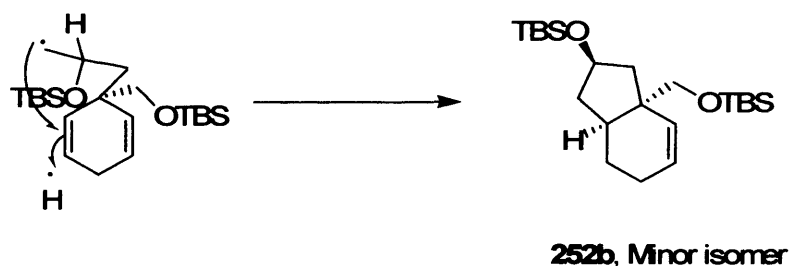
**Scheme 143** *Reagents and Conditions:* (i) **251**, dry benzene, AIBN,  $\text{Bu}_3\text{SnH}$ , reflux 30 h.

Although compound **252** was not fully characterised due to the fact that the reaction was carried out on a very small scale, the structure was completely established by  $^1\text{H}$ ,  $^{13}\text{C}$  NMR data and comparison with related compounds. With regard to the stereochemistry of compound **252** the major isomer is most likely to be as shown in **Figure 9** based on structural models as the OTBS group will prefer to be in a *pseudo*-equatorial position in the envelop conformation of the new 5-membered ring. This will lead to attack on the right-hand double-bond, giving the stereochemistry shown.



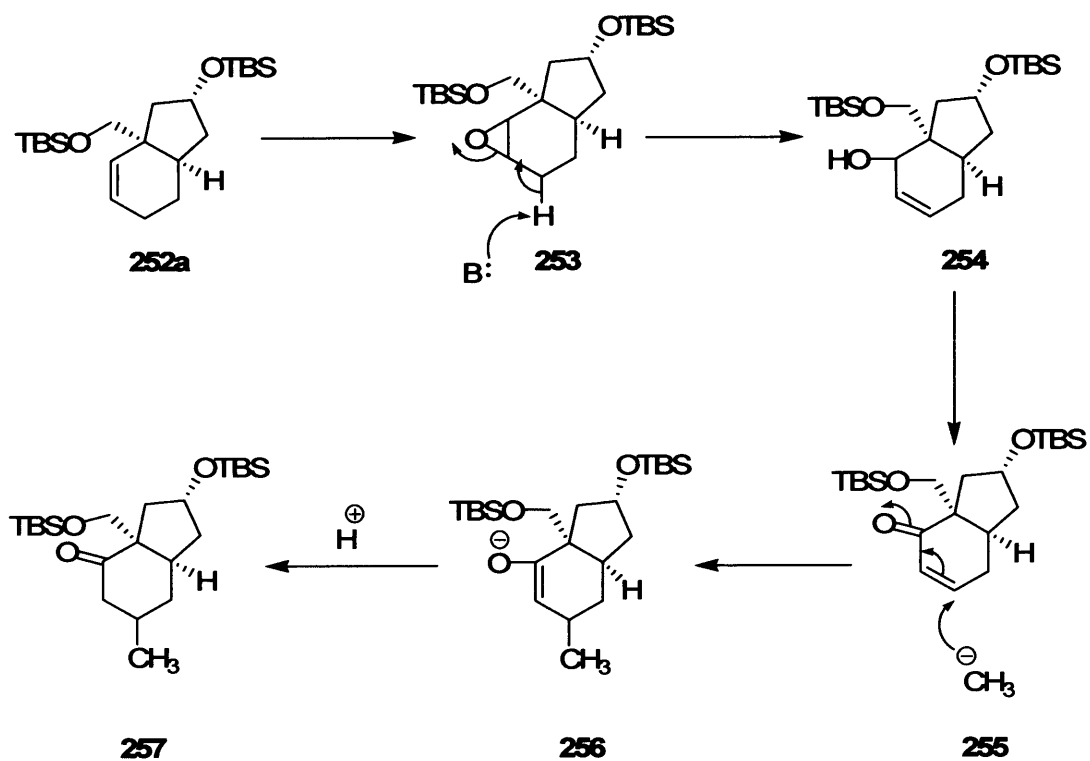
**Figure 9** The expected stereochemistry of the major isomer **252a**

On the other hand the minor isomer **252b** might be possibly formed as a result of free-radical attack on the left-hand side double-bond. In this case, isomer **252b** would suffer from some unfavourable interactions between the bulky TBS group and the cyclohexene ring (**Figure 10**).



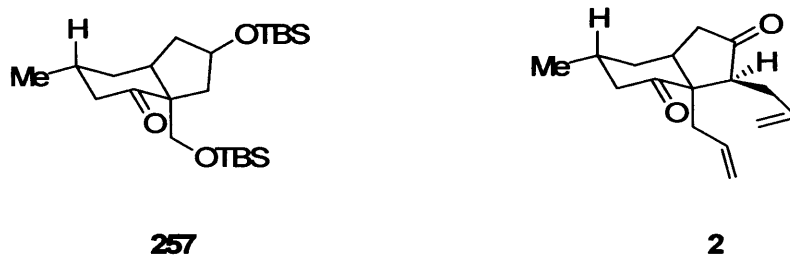
**Figure 10** The expected stereochemistry of the minor isomer **252b**

In fact, this chemistry was carried out during the final weeks of the project, so we had no time to pursue the synthesis. However, the introduction of the methyl and the ketone groups onto the 6-membered ring might be accomplished by using epoxide chemistry. In principle epoxidation of the remaining double bond of compound **252a** will result in epoxide **253** which may be opened using a base to afford allylic alcohol **254**. Oxidation of the allylic hydroxyl group will result in the formation of enone **255**. Conjugate addition to enone **255** will provide the bicyclic enolate **256** which will be protonated to give the ketone **257** (**Scheme 144**).



**Scheme 144** The possible path way to prepare analogue to the key fragment 2

This target enone **257** has a very similar structure to the key fragment **2**.



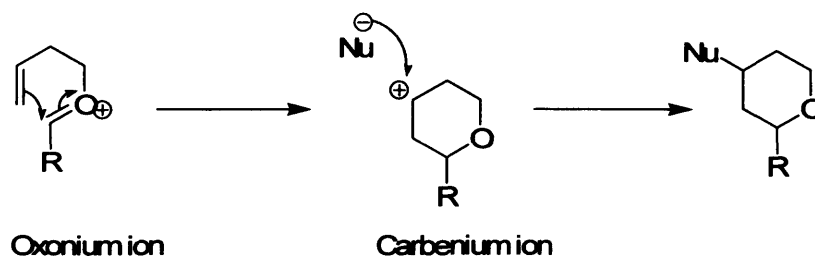
## **Chapter 5**

# **Lewis Acid-promoted Diastereoselective Prins Reactions of Cyclohexa-1,4-dienes**

[Through out this chapter, single enantiomer stereochemistries of the precursors for the Prins cyclisation reactions are indicated by dashes or wedges to indicate the stereogenic centre, but all are racemates. When there is more than one stereogenic centre, the relative stereochemistries proposed are based either on X-ray data, NMR studies and/or mechanistic speculations: in all such cases, the compounds are also racemates].

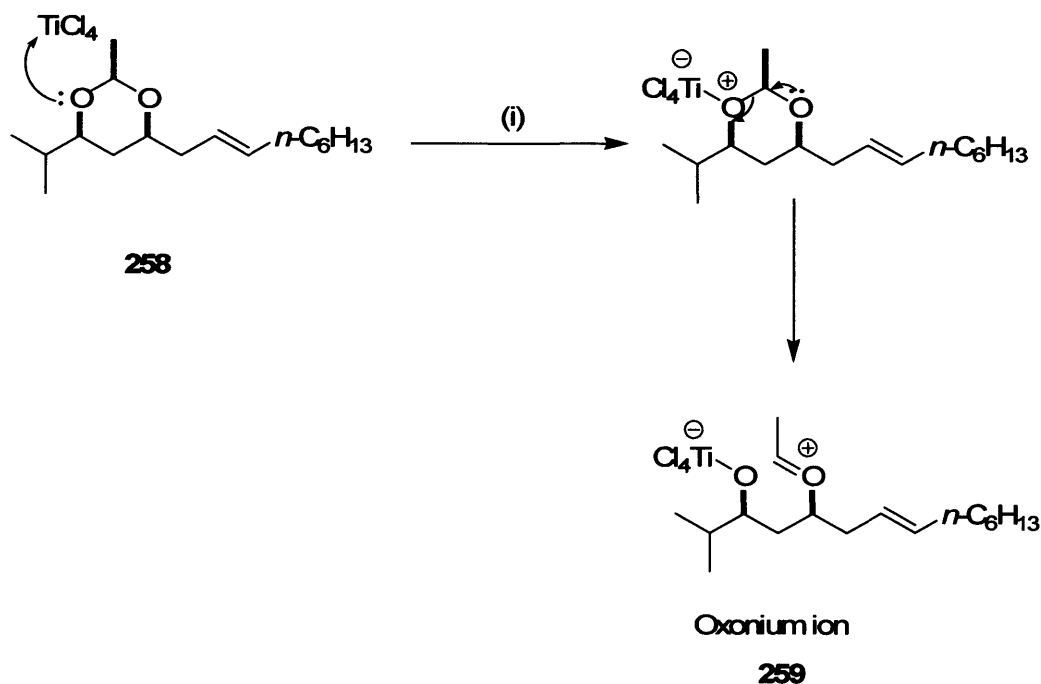
### 5.1. Introduction

In general, the reaction of an alkene with an oxonium ion is called the Prins reaction as shown in **Scheme 145**.<sup>73</sup>



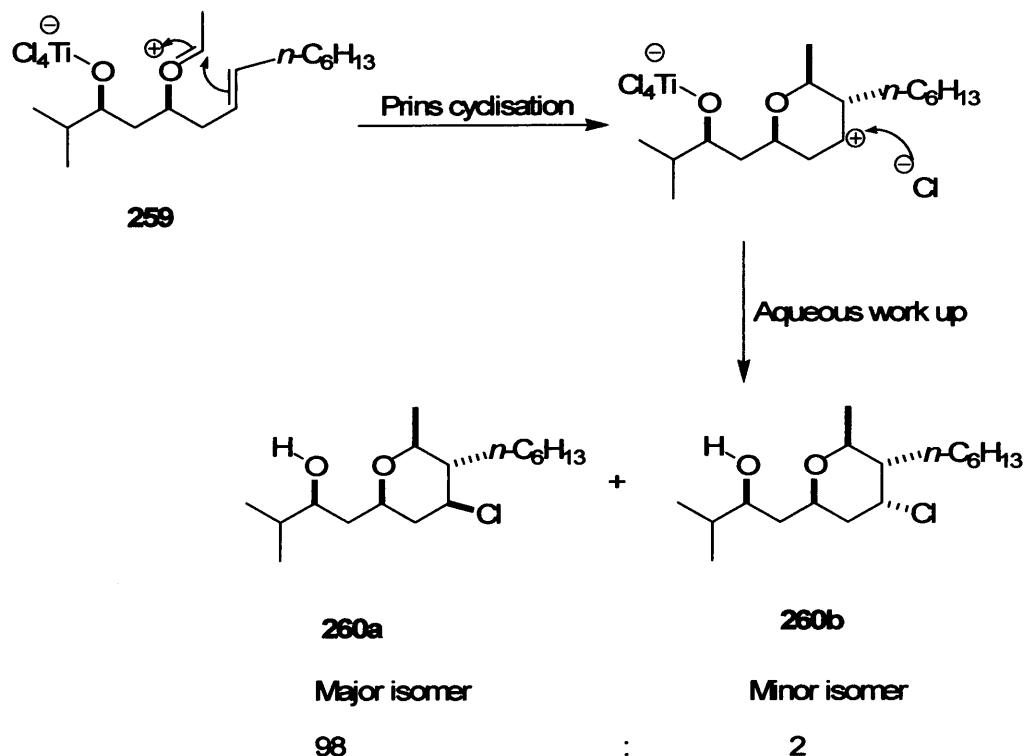
**Scheme 145**

These reactive oxonium ions have been generated by a number of different methods. One of these methods involved ionisation of acetals using Lewis acids as demonstrated by Rychnovsky and his group. They showed that treatment of allylic acetal **258** with a strong Lewis acid resulted in the formation of oxonium ion **259** (**Scheme 146**).<sup>74</sup>



**Scheme 146** *Reagents and conditions:* (i)  $\text{TiCl}_4$ , 2 equiv.,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 2 h.

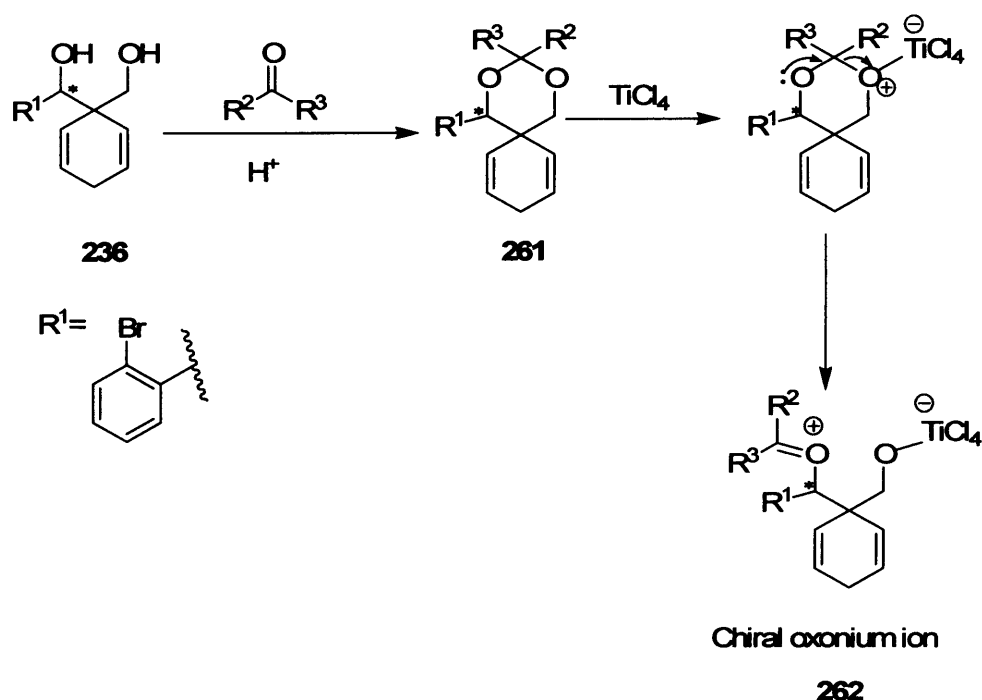
This intermediate ion underwent Prins cyclisation followed by nucleophilic capture of the resultant tetrahydropyranyl cation to afford tetrahydropyran rings **260a** and **260b** in high yield and high diastereoselectivity (major:minor ratio 98:2) (**Scheme 147**).



**Scheme 147**

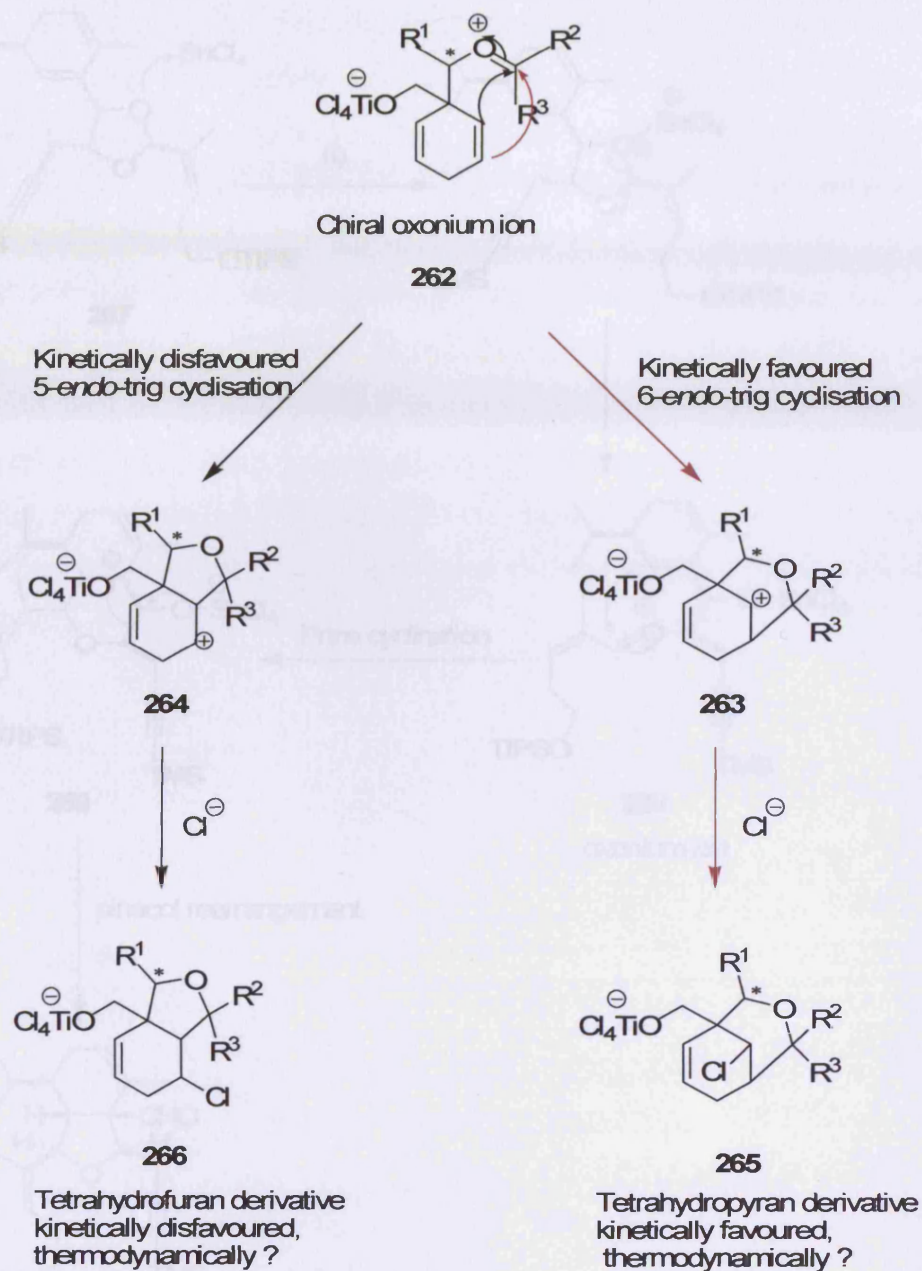
Based on this result and the availability of diol **236** (which was a precursor for the free-radical cyclisation reactions described in Chapter 4) we decided to investigate the possibility of using the same concept to desymmetrise the two diastereotopic double bonds of cyclohexadiene derivatives. Previously we have desymmetrised the two diastereotopic double bonds of cyclohexadiene derivatives *via* nucleophilic addition reactions as shown in Chapter 2 and through free-radical reactions as explained in Chapter 4. In this case the desymmetrisation process will proceed *via* diastereoselective electrophilic attack on one of the two diastereotopic double bonds by the oxonium ion which will be generated under the reaction conditions. Initially, the diol **236** would be transformed to acetal **261** and then treated with a Lewis acid. This should result in the formation of oxonium ion **262** (**Scheme 148**).





**Scheme 148**

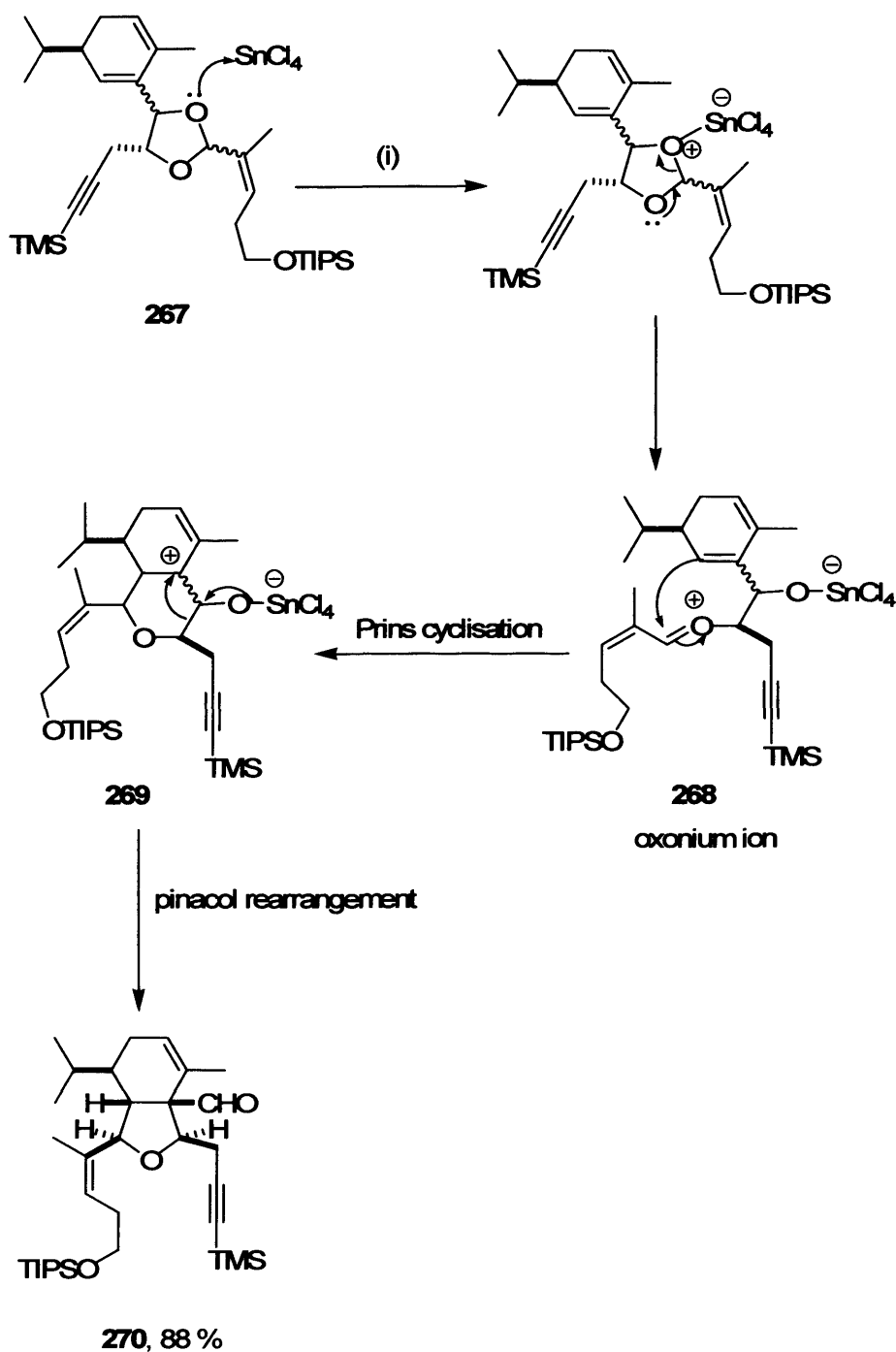
This intermediate is a chiral species; therefore it could be able to differentiate between the two diastereotopic double bonds and control the diastereoselectivity of the subsequent Prins cyclisation step. There is also the issue of regioselectivity. The oxonium ion could, in principle, attack either end of the double bond. However, formation of tetrahydropyran derivatives **265** should be favoured over tetrahydrofuran **266** according to Baldwin's rules since 6-*endo*-trig cyclisation is favoured over a 5-*endo*-trig cyclisation. However, the outcome of this reaction can not be definitely predicted since it is known that Baldwin's rules generally describe the kinetic favourability and there are some cases where the 5-*endo*-trig cyclisation proceeds smoothly especially when a reaction involves cations or it is thermodynamically very favourable (Scheme 149).<sup>75</sup>



**Scheme 149**

Other rearranged products may be produced since Prins cyclisation is sometimes followed by pinacol rearrangement and in this case tetrahydrofuran derivatives are formed. For example, Overman and Pennington<sup>76</sup> reported stereoselective  $\text{SnCl}_4$  promoted Prins cyclisation-pinacol rearrangement sequence of acetal **267** which resulted in the formation of tetrahydrofuran derivative **270** in 88 % yield (**Scheme 150**).

Additionally, several authors have reported the oxonia-Cope rearrangement as a competitive process in the Prins cyclisations which resulted in the formation of

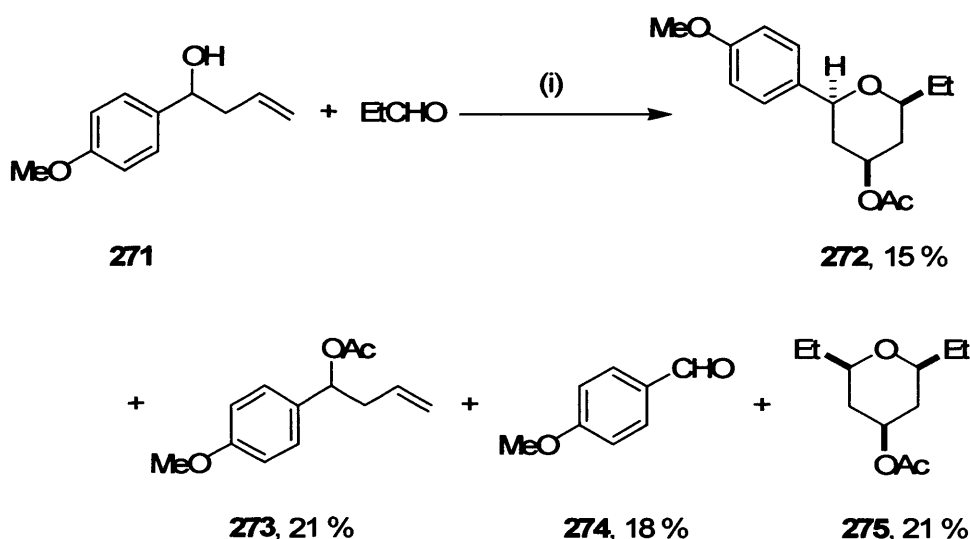


**Scheme 150** Reagents and conditions: (i) 10 mol %  $\text{SnCl}_4$ , 1:1  $\text{CH}_2\text{Cl}_2/\text{MeNO}_2$ ,  $-50^\circ\text{C}$ , 1.5 h.

As shown in the previous scheme, the driving force for the pinacol rearrangement is the  $\alpha$ -oxygen atom.

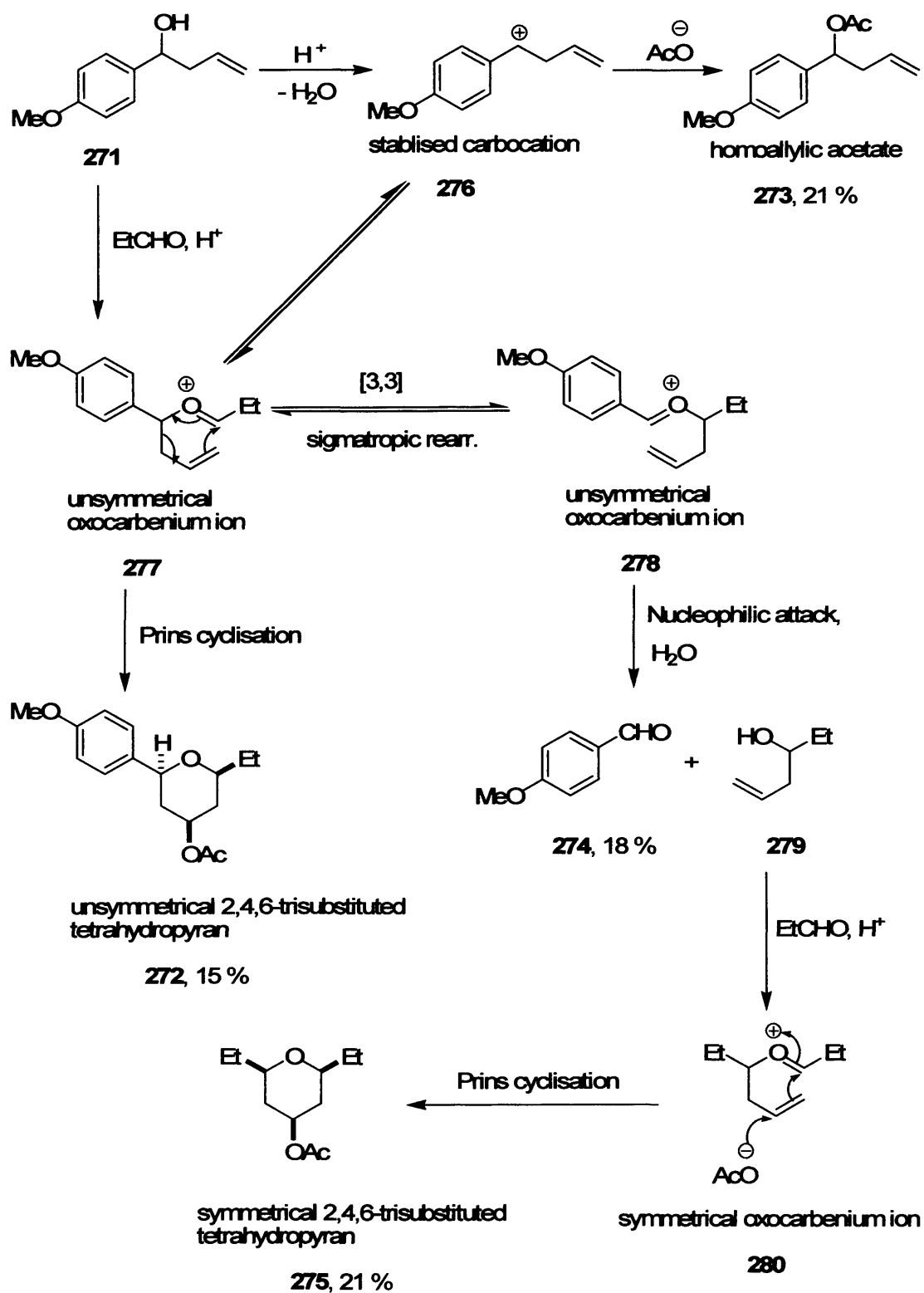
Additionally, several authors have reported the oxonia-Cope rearrangement as a competitive process in the Prins cyclisations which resulted in the formation of

unexpected products. For example, Willis and co-workers<sup>77</sup> demonstrated that the reaction between an oxocarbenium ion, generated *in situ* from the reaction of homoallylic alcohol having a side chain with an electron-rich aromatic ring, would favour oxonia-Cope rearrangement through stabilisation of the positive charge. Therefore the cyclisation of the electron-rich anisaldehyde-derived homoallylic alcohol **271** with propanal using BF<sub>3</sub>·OEt<sub>2</sub> (2 equiv.) in the presence of AcOH (5 equiv.) and TMSOAc (4 equiv.) in cyclohexane at room temperature resulted in formation of the expected Prins trisubstituted tetrahydropyran **272** as a single diastereoisomer in only 15 % yield. Surprisingly, three other products were isolated including the homoallylic acetate **273**, the parent aldehyde **274** and finally the unexpected symmetrical 2,4,6-trisubstituted tetrahydropyran **275** in comparatively higher yield as shown in **Scheme 151**.



**Scheme 151** Reagents and conditions: (i) BF<sub>3</sub>·Et<sub>2</sub>O, AcOH, TMSOAc, C<sub>6</sub>H<sub>12</sub>, r.t., 2 h.

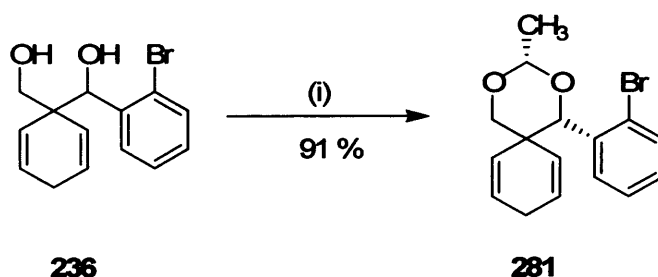
Formation of the symmetrical tetrahydropyran **275** was very surprising for the authors since this was the first example of Prins-type cyclisation involving a homoallylic alcohol and an aldehyde having different side chains to give rise to a symmetrical product. They proposed a mechanism involving oxonia-Cope rearrangement to account for the formation of compounds **274** and **275**. However, for the formation of homoallylic acetate **273**, a stabilised carbocation intermediate **276** was implicated as shown in **Scheme 152**.



**Scheme 152**

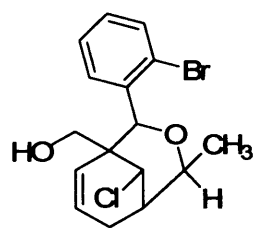
Finally, in accord with investigating the Prins cyclisation reaction of cyclohexadiene-derived acetals, the nature of the substituents  $\text{R}^1$ ,  $\text{R}^2$ , and  $\text{R}^3$  in

oxonium ion **262** may affect the diastereoselectivity and the outcome of the cyclisation step; however, a simple substrate is needed to examine the key bond forming reactions. Therefore the diol **236** was protected as an acetaldehyde acetal **281** which was formed as a single diastereoisomer (**Scheme 153**).

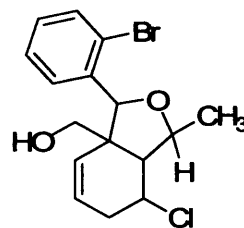


**Scheme 153** *Reagents and conditions:* (i) MeCHO, CH<sub>2</sub>Cl<sub>2</sub>, pyridinium *p*-toluenesulfonate, r.t., 72 h.

Prins cyclisation was initially investigated using two equivalents of TiCl<sub>4</sub> as Lewis acid at -78 °C for 4 hours. This resulted in the formation of three compounds in major:minor:minor ratio of 5.5:1.0:1.0. Purification of the crude reaction mixture was very difficult since TLC showed many spots having very close R<sub>f</sub> values but at the end two pure compounds were isolated, but neither of which was the major compound in the crude reaction mixture. The first fraction being eluted from the column was initially identified as an alcohol. This assignment was based on the presence of two diastereotopic protons at  $\delta = 3.60$  and 3.22 ppm which corresponded to a CH<sub>2</sub> group adjacent to an oxygen atom. Also the two remaining alkene protons were quite obvious. These observations were confirmed by counting the number of the CH and CH<sub>2</sub> groups in the <sup>13</sup>C NMR spectrum. As illustrated in **Scheme 149**, direct Prins cyclisation can lead to the formation of tetrahydropyran or tetrahydrofuran derivatives depending on which end of each double bond will be attacked by the intermediate oxonium ion. Therefore there were two proposed structures for this compound, either tetrahydropyran **282** or tetrahydrofuran **283**

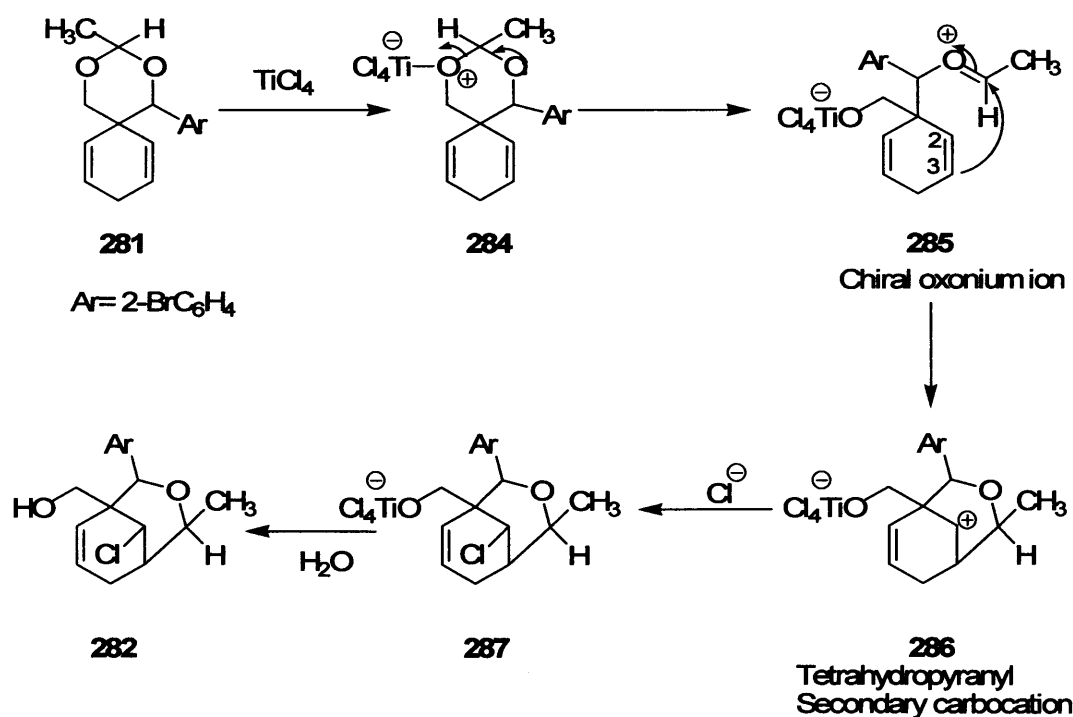


**282**



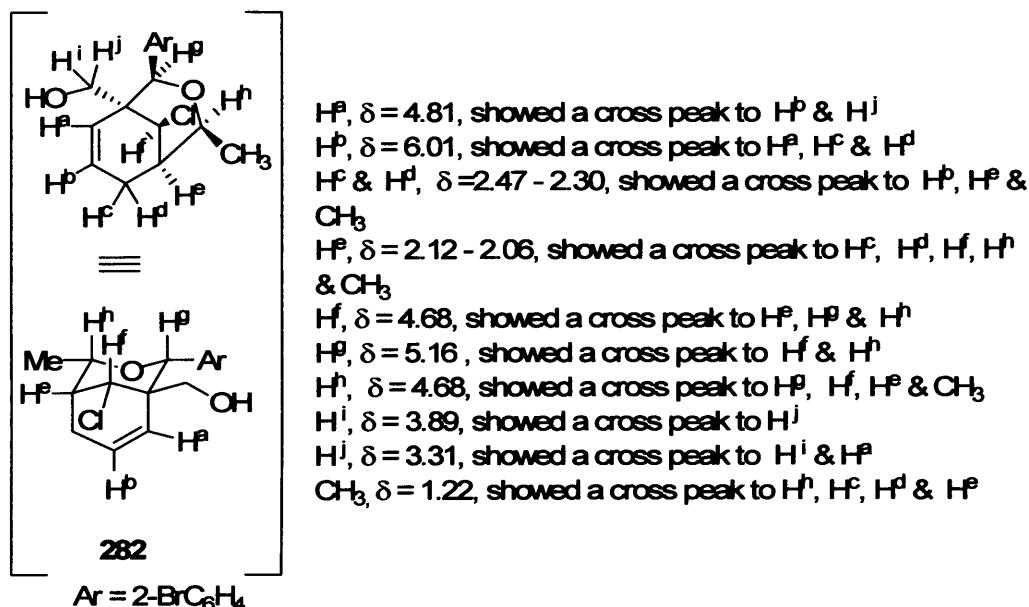
**283**

This compound was identified as the one of the minor compounds in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture and its spectroscopic data including  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR,  $^1\text{H}$  -  $^1\text{H}$  and  $^1\text{H}$  -  $^{13}\text{C}$  correlation spectra were more consistent with structure **282**. This is mainly because the diagnostic peak at  $\delta = 4.68$  ppm which is identified as the proton attached to the carbon bearing the chlorine atom did not give a cross peak to the allylic methylene protons in the  $^1\text{H}$  -  $^1\text{H}$  COSY experiment, which would not be expected if it has structure **283**. Also structure **282** is supported by the crystal structure determination of a related compound as will be discussed later. From the mechanistic point of view compound **282** is formed through the favoured 6-*endo*-trig attack at the further end of the double bond (at C-3) followed by capture of the nucleophilic chloride ion at the secondary carbocation centre formed at the other end of the double bond (C-2) as shown in **Scheme 154**.



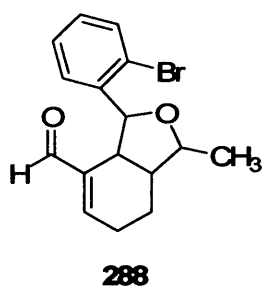
**Scheme 154**

The NOESY experiments revealed the following correlations which identified the relative stereochemistry of the newly formed tetrahydropyran ring as shown below.

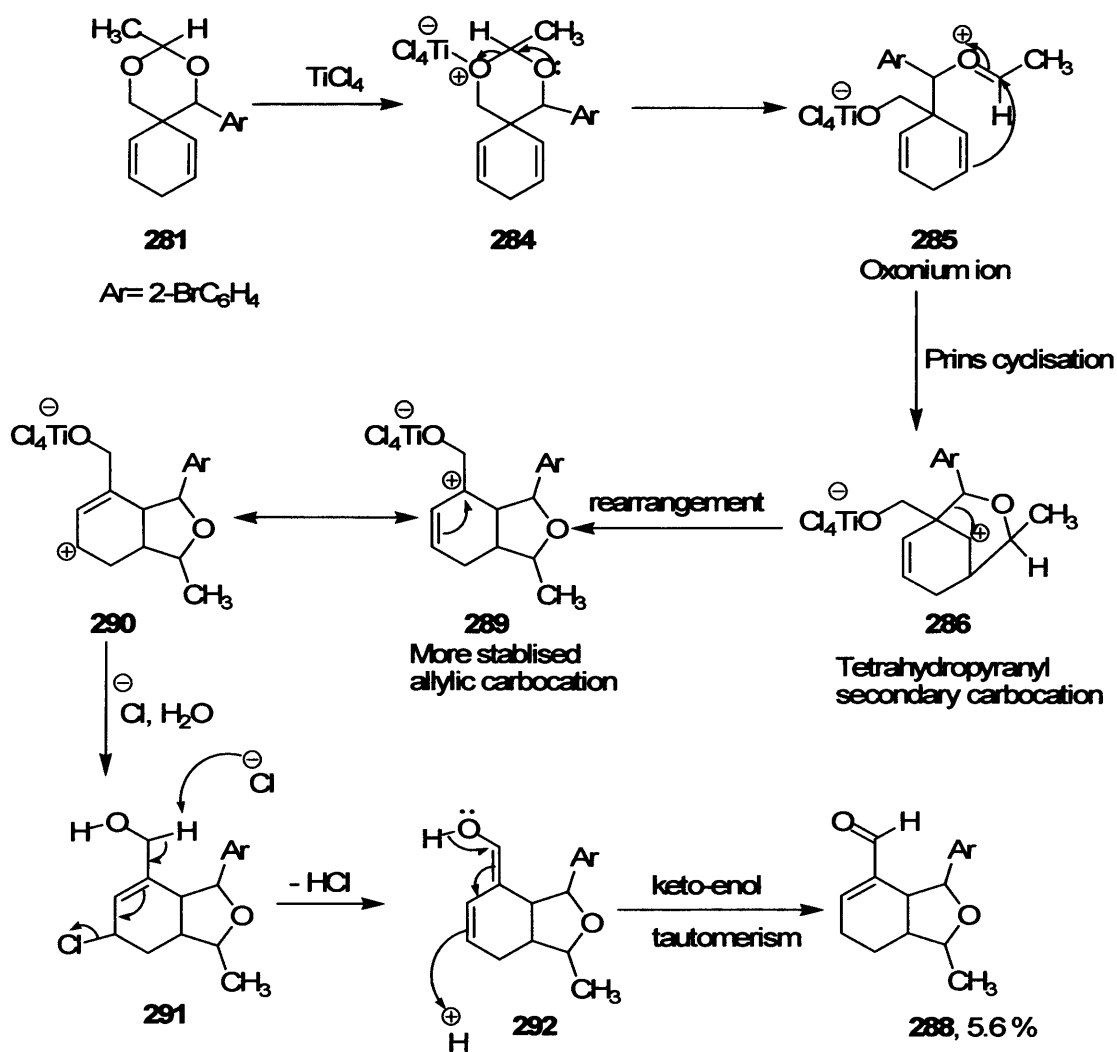


The second compound to be eluted from the column was also one of the minor products in the crude reaction mixture. In this case this compound was initially identified as an aldehyde due to the presence of an aldehyde proton at  $\delta = 8.79$  ppm in the  $^1\text{H}$  NMR spectrum and an aldehydic CH group at  $\delta = 192.2$  ppm in the  $^{13}\text{C}$  NMR spectrum. The structure was eventually assigned as compound **288** based on the following observations in the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. Only one alkene CH was present in the  $^1\text{H}$  NMR spectrum. This has a high chemical shift value indicating  $\beta$ -conjugated CH. This is supported by the presence of three quaternary carbons in the  $^{13}\text{C}$  NMR spectrum (in the region between  $142 - 120$  ppm.). Two of them correspond to the two quaternary aromatic carbons and the third one corresponds to the quaternary alkene carbon. The presence of four CH carbons; two of these are joined to oxygen in tetrahydrofuran ring. The remaining two upfield CH groups (at  $\delta = 39.8$  and  $39.5$  ppm) correspond to the two ring junction CH carbons. Finally, there were two aliphatic  $\text{CH}_2$  carbons. This confirmed the structure as a rearrangement product which does not have a chlorine atom.



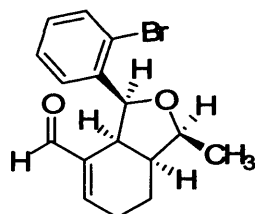


The formation of this compound can be rationalised as below (**Scheme 155**). The driving force for this rearrangement is to form the more stabilised allylic carbocation **289**.



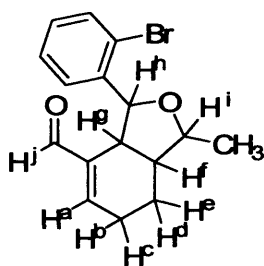
**Scheme 155**

Finally, the structure of this compound and the relative stereochemistry were confirmed by a combination of  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, HRMS,  $^1\text{H} - ^1\text{H}$  COSY, NOESY, and  $^1\text{H} - ^{13}\text{C}$  correlation spectra to be as shown below.



**288**

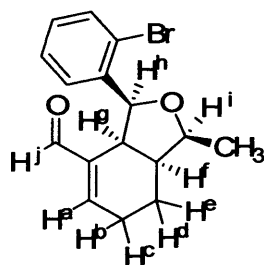
$^1\text{H} - ^1\text{H}$  COSY experiment showed the following correlations



**288**

$\text{H}^a$ ,  $\delta = 6.75$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^c$  &  $\text{H}^d$   
 $\text{H}^b$ ,  $\delta = 2.45$ , showed a cross peak to  $\text{H}^a$ ,  $\text{H}^c$ ,  $\text{H}^d$  &  $\text{H}^e$   
 $\text{H}^c$ ,  $\delta = 2.24 - 2.13$ , showed a cross peak to  $\text{H}^a$ ,  $\text{H}^b$ ,  $\text{H}^d$  &  $\text{H}^e$   
 $\text{H}^d$  &  $\text{H}^e$ ,  $\delta = 1.80 - 1.63$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^c$  &  $\text{H}^f$   
 $\text{H}^f$ ,  $\delta = 2.32 - 2.24$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^i$ ,  $\text{H}^d$  &  $\text{H}^e$   
 $\text{H}^g$ ,  $\delta = 3.60 - 3.53$ , showed a cross peak to  $\text{H}^h$ ,  $\text{H}^f$  &  $\text{H}^i$   
 $\text{H}^h$ ,  $\delta = 5.54$ , showed a cross peak to  $\text{H}^g$   
 $\text{H}^i$ ,  $\delta = 4.07$ , showed a cross peak to  $\text{H}^f$  &  $\text{CH}_3$   
 $\text{CH}_3$ ,  $\delta = 1.31$ , showed a cross peak to  $\text{H}^i$

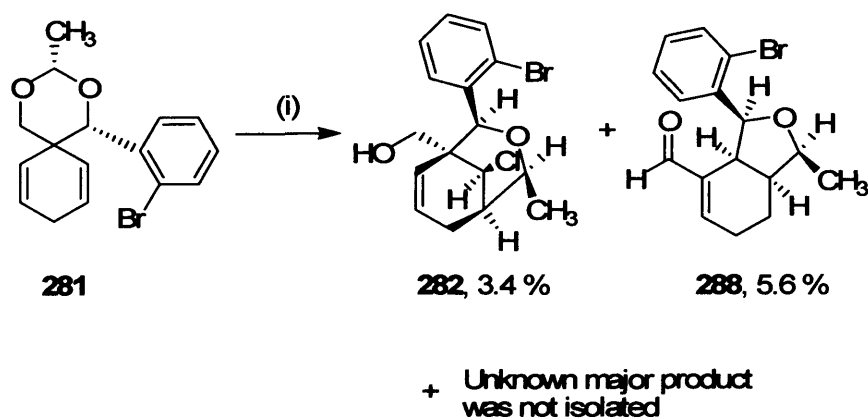
NOESY experiment showed the following correlations



**288**

$\text{H}^a$ ,  $\delta = 6.75$ , showed a cross peak to  $\text{H}^j$ ,  $\text{H}^b$  &  $\text{H}^c$   
 $\text{H}^b$ ,  $\delta = 2.45$ , showed a cross peak to  $\text{H}^a$ ,  $\text{H}^c$ ,  $\text{H}^d$  &  $\text{H}^e$   
 $\text{H}^c$ ,  $\delta = 2.24 - 2.13$ , showed a cross peak to  $\text{H}^a$ ,  $\text{H}^b$ ,  $\text{H}^d$  &  $\text{H}^e$   
 $\text{H}^d$  &  $\text{H}^e$ ,  $\delta = 1.80 - 1.63$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^c$ ,  $\text{H}^f$ , two of aromatic H at  $\delta = 7.11 - 7.04$  &  $\text{CH}_3$   
 $\text{H}^f$ ,  $\delta = 2.32 - 2.12$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^i$ ,  $\text{H}^d$  &  $\text{H}^e$   
 $\text{H}^g$ ,  $\delta = 3.60 - 3.53$ , showed a cross peak to  $\text{H}^h$ ,  $\text{H}^f$  &  $\text{H}^i$   
 $\text{H}^h$ ,  $\delta = 5.54$ , showed a cross peak to  $\text{H}^g$  &  $\text{H}^i$   
 $\text{H}^i$ ,  $\delta = 4.07$ , showed a cross peak to  $\text{H}^f$ ,  $\text{H}^h$ ,  $\text{H}^g$  &  $\text{CH}_3$   
 $\text{H}^j$ ,  $\delta = 8.79$ , showed a cross peak to  $\text{H}^a$   
 $\text{CH}_3$ ,  $\delta = 1.31$ , showed a cross peak to  $\text{H}^i$ ,  $\text{H}^d$  &  $\text{H}^e$

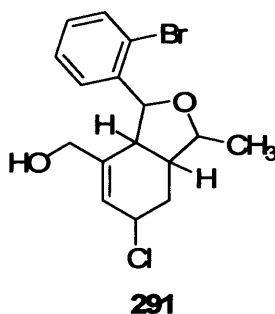
Thus the outcome of the first Prins reaction of acetaldehyde acetal **281** can be summarised as in Scheme 156.



**Scheme 156** Reagents and conditions: (i)  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 4 h.

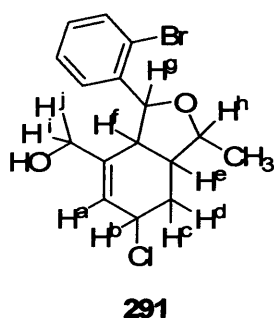
Since the major product was not isolated in the initial experiment the reaction was repeated under the same conditions but only for two hours and the same result was obtained. The  $^1\text{H}$  NMR spectrum of the crude reaction mixture showed the presence of the same major and two minor products as in the previous experiment. In the initial experiments the products were purified by chromatography on silica gel with considerable loss of material. To avoid this loss, crystallisation was tried but unfortunately it did not work. However, the obtained spectroscopic data of this crude reaction mixture was sufficiently clear, and by combination with the results obtained from another experiment as will be discussed later, this compound was fully identified. The crude  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra revealed the following features. The absence of any aldehyde proton in the  $^1\text{H}$  NMR spectrum which could correspond to the major isomer. This was supported by the absence of an aldehyde CH group in the  $^{13}\text{C}$  NMR spectrum. The presence of two diastereotopic protons corresponding to the  $\text{CH}_2$  group adjacent to an oxygen atom as indicated from the  $^{13}\text{C}$  NMR spectrum ( $\delta = 64.7$  ppm). Therefore this product appears to be an alcohol. Also the obtained data indicated the presence of only one alkene CH which was attributed to the fact that the other alkene carbon is a quaternary centre; *i.e.* it is the point where the alcohol side chain is attached. This assumption was supported by the presence of five aliphatic CH carbons in the  $^{13}\text{C}$  NMR spectrum, three of these are joined to electronegative elements (O and Cl atoms), and the remaining two CH carbons are consistent with ring junction CH groups as in compound **288**. Moreover, the fact that the benzylic CH proton is a doublet rather than just a singlet confirms the structure as a rearranged product lacking the quaternary stereogenic centre. All these data support alcohol **291** as the proposed structure for the major product produced during the

reaction. Alcohol **291** seemed to be formed through the kinetically favoured 6-*endo*-trig cyclisation followed by rearrangement. This compound then can undergo elimination/tautomerisation to give aldehyde **288** as shown above in **Scheme 155** (page 121).



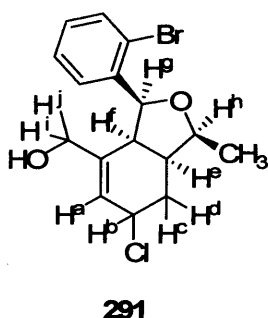
The  $^1\text{H} - ^1\text{H}$  COSY experiment confirmed the structure of alcohol **291** as indicated by the following correlations, particularly the cross peak between  $\text{H}^b$  and  $\text{H}^a$  and the cross peak between  $\text{H}^g$  (the benzylic proton) and  $\text{H}^f$  (the adjacent ring junction proton).

Additionally the  $^1\text{H} - ^1\text{H}$  COSY spectrum showed the following correlations



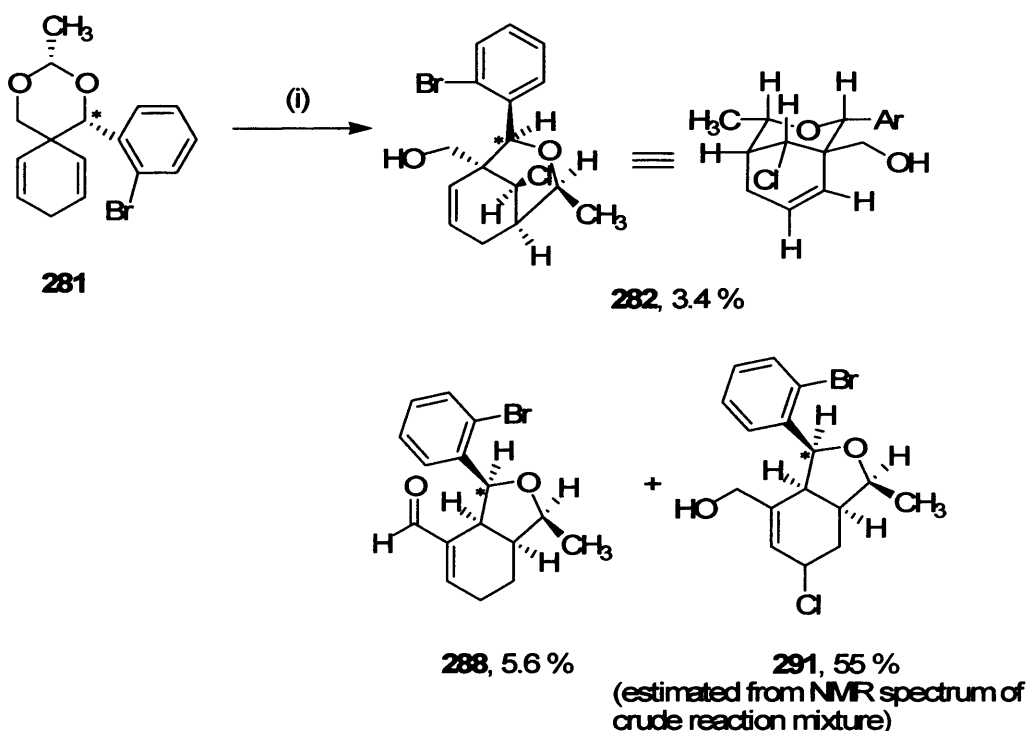
$\text{H}^a$ ,  $\delta = 5.84$ , showed a cross peak to  $\text{H}^b$  &  $\text{H}^f$   
 $\text{H}^b$ ,  $\delta = 4.72 - 4.64$ , showed a cross peak to  $\text{H}^a$ ,  $\text{H}^f$  &  $\text{H}^d$   
 $\text{H}^f$  &  $\text{H}^d$ ,  $\delta = 2.15 - 2.20$ , showed a cross peak to  $\text{H}^b$  &  $\text{H}^e$   
 $\text{H}^e$ ,  $\delta = 2.70 - 2.61$ , showed a cross peak to  $\text{H}^f$ ,  $\text{H}^d$ ,  $\text{H}^g$  &  $\text{H}^h$   
 $\text{H}^g$ ,  $\delta = 5.41$ , showed a cross peak to  $\text{H}^f$   
 $\text{H}^h$ ,  $\delta = 4.10$ , showed a cross peak to  $\text{H}^e$  &  $\text{CH}_3$   
 $\text{H}^i$ ,  $\delta = 3.48$ , showed a cross peak to  $\text{H}^j$   
 $\text{H}^j$  &  $\text{H}^f$ ,  $\delta = 3.35 - 3.28$ , showed a cross peak to  $\text{H}^i$ ,  $\text{H}^a$ ,  $\text{H}^g$  &  $\text{H}^e$   
 $\text{CH}_3$ ,  $\delta = 1.30$ , showed a cross peak to  $\text{H}^h$

NOESY experiment showed the following correlations



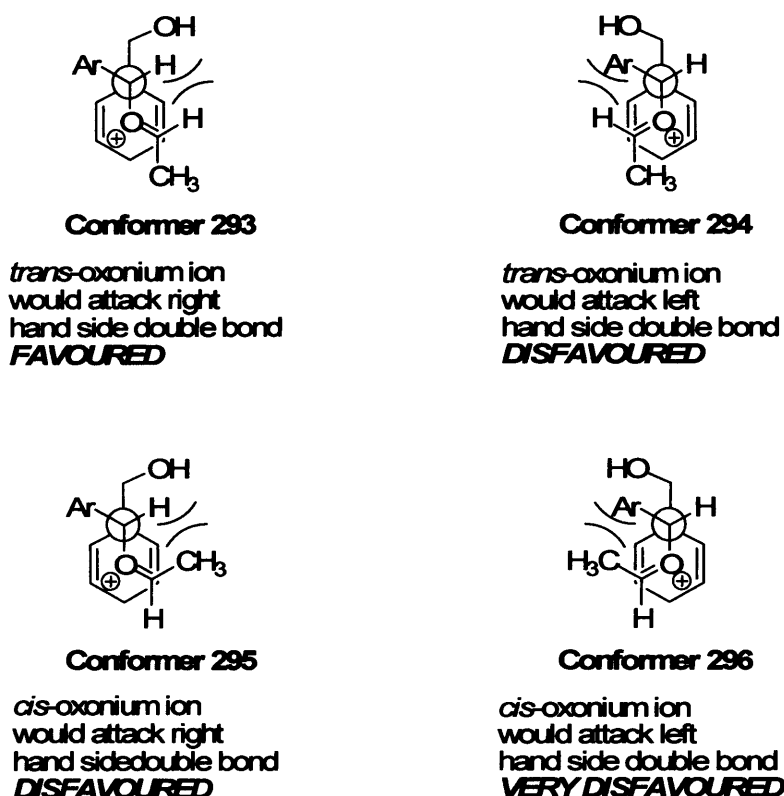
$\text{H}^a$ ,  $\delta = 5.84$ , showed a cross peak to  $\text{H}^b$   
 $\text{H}^b$ ,  $\delta = 4.72 - 4.64$ , showed a cross peak to  $\text{H}^a$ ,  $\text{H}^f$  &  $\text{H}^d$   
 $\text{H}^f$  &  $\text{H}^d$ ,  $\delta = 2.15 - 2.20$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^e$  &  $\text{CH}_3$   
 $\text{H}^e$ ,  $\delta = 2.70 - 2.61$ , showed a cross peak to  $\text{H}^f$ ,  $\text{H}^d$ ,  $\text{H}^g$  &  $\text{H}^h$   
 $\text{H}^g$ ,  $\delta = 5.41$ , showed a cross peak to  $\text{H}^f$  &  $\text{H}^e$   
 $\text{H}^h$ ,  $\delta = 4.10$ , showed a cross peak to  $\text{H}^e$ ,  $\text{H}^f$ ,  $\text{H}^g$  &  $\text{CH}_3$   
 $\text{H}^i$ ,  $\delta = 3.48$ , showed a cross peak to  $\text{H}^j$   
 $\text{H}^j$  &  $\text{H}^f$ ,  $\delta = 3.35 - 3.28$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^h$ ,  $\text{H}^i$  &  $\text{H}^e$   
 $\text{CH}_3$ ,  $\delta = 1.30$ , showed a cross peak to  $\text{H}^h$ ,  $\text{H}^f$  &  $\text{H}^d$

Thus the outcome of the kinetic Prins cyclisation of acetaldehyde acetal **281** can be summarised as shown in **Scheme 157**.



**Scheme 157** *Reagents and conditions:* (i)  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 4 h.

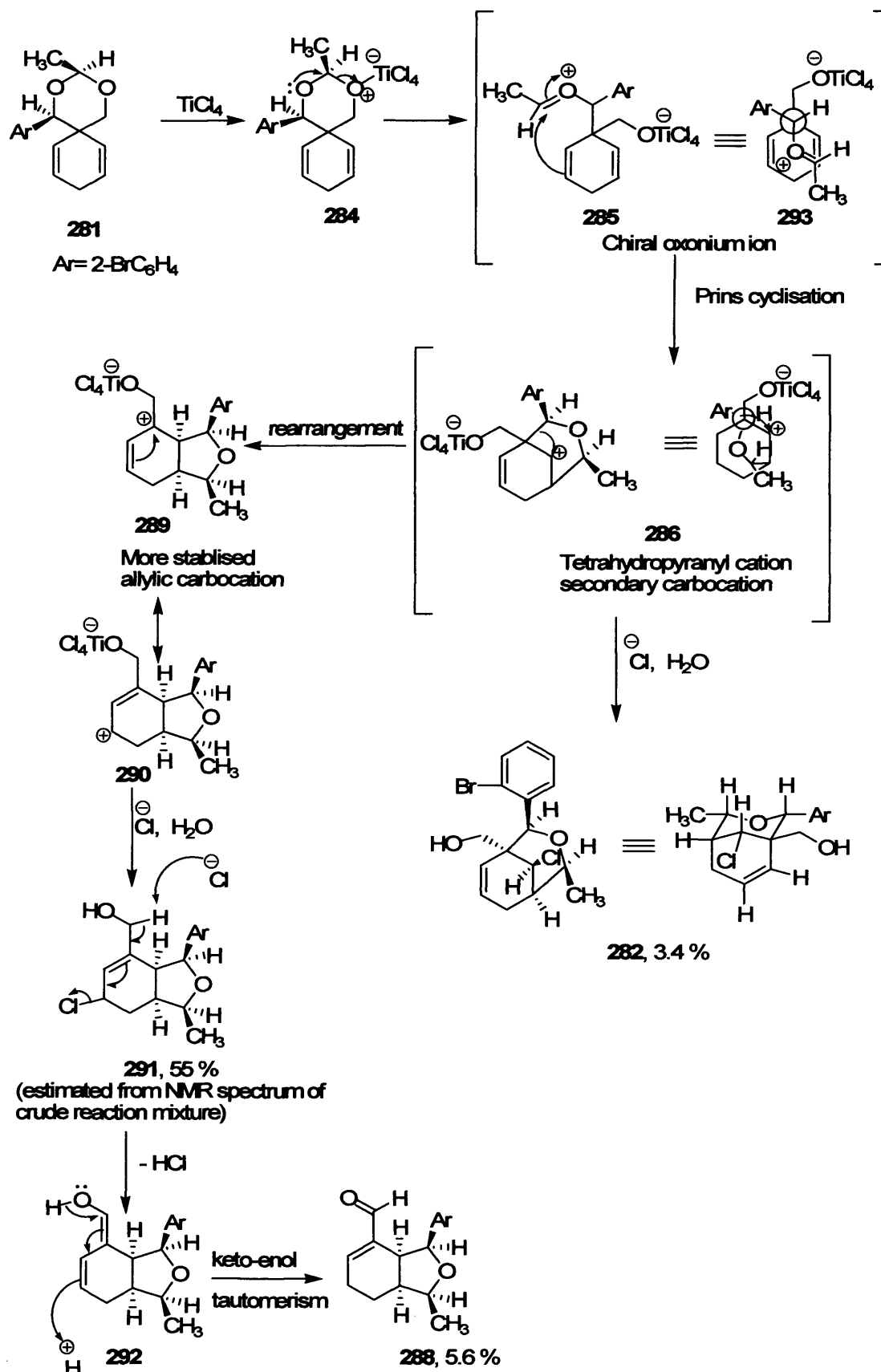
As can be observed from **Scheme 157** all the products obtained from the Prins cyclisation of acetaldehyde acetal **281** under the above conditions have a *cis* relationship between the original stereogenic centre (indicated with asterisk) and all the newly formed stereogenic centres. Additionally, all of these products resulted *via* the electrophilic attack of the oxonium ion on the right-hand side double-bond. These observations can be rationalised as follows: As the oxonium ion formed there are two factors would control the subsequent cyclisation step. The first is the geometry of the double bond bearing the oxocarbenium ion. The second is the choice of which double bond would be attacked under the influence of the existing stereogenic centre. Base on these factors there are four possible transition state models (conformers **293**, **294**, **295**, and **296**) as shown in **Scheme 158**.



**Scheme 158**

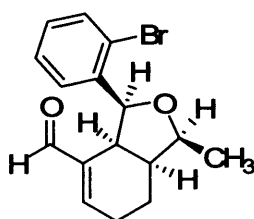
The transition state models presented in **Scheme 158** suggested that conformer **293** would be favoured over all the other models. Conformer **293** would suffer from the least destabilising interaction since in this case the  $A^{1,3}$ -strain is between two hydrogen atoms, whereas in conformer **294** this destabilising interaction is between the aryl side chain and the hydrogen atom. Also conformer **295** would suffer from this destabilising interaction between the methyl group and the hydrogen atom. Finally, conformer **296** would suffer from the highest destabilising interaction since it is between two bulky substituents (the aryl group and the methyl group). Therefore it can be strongly assumed that the cyclisation step took place through conformer **293** to afford tetrahydropyranyl cation **286** which could capture a chloride ion to afford compound **282** with the observed stereochemistry. Alternatively, this tetrahydropyranyl cation could undergo rearrangement without inversion of the stereochemistry to provide the more stabilised allylic carbocation **290** that in turn would abstract a chloride ion to afford compound **291** having the same relative stereochemistry as compound **282**. Finally, compound **291** which seemed to be very unstable might be transformed to aldehyde **288** with the same relative

stereochemistry through elimination of HCl followed by keto-enol tautomerism. All of these processes can be summarised in **Scheme 159**.



**Scheme 159**

The Prins reaction of acetaldehyde acetal **281** was repeated by stirring this compound with two equivalents of  $\text{TiCl}_4$  at  $-78\text{ }^\circ\text{C}$  for one hour then at room temperature for 23 h. This resulted in a cleaner reaction. Because the purification process of the cyclohexadiene products was generally not an easy task and led to low yields, it was better to analyse the spectroscopic data of the crude reaction mixture which was cleaner than those obtained in the previous experiments before attempting the purification. The  $^1\text{H}$  NMR spectrum of the crude reaction mixture showed the presence of two aldehydes, as indicated by the presence of two aldehyde protons of major:minor ratio 5.2: 1.0. This was accompanied by the absence of any diastereotopic  $\text{CH}_2$  protons attached to an oxygen atom (*i.e.* no alcohol group). Additionally there was only one alkene proton for each compound; the major peak gave more hyperfine splittings whereas the minor peak was a simple doublet. The major compound showed similar, but not identical, features to compound **288**, and so appeared to be a stereoisomer.

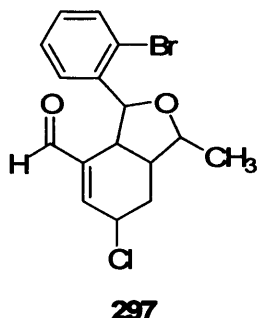


**288**

Purification by flash chromatography afforded two products. The first one was identified as the minor in the crude reaction mixture which was previously assumed to be an aldehyde. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of this fraction established that it is really an aldehyde as indicated by the following characteristic features. The presence of an aldehyde proton at  $\delta = 9.38$  ppm and an aldehyde CH group at  $\delta = 191.2$  ppm. The alkene proton is a simple doublet at  $\delta = 6.74$  ppm indicating that there is only one adjacent proton to it. This is supported by the presence of three quaternary carbons in the  $^{13}\text{C}$  NMR spectrum which are corresponding to the two quaternary aromatic carbons and the quaternary alkene carbon. The presence of five aliphatic CH groups; two of these attached to the oxygen atom of the tetrahydrofuran ring, two ring junction CH groups and the remaining one corresponds to a CH carbon attached to a chlorine atom as indicated by the high chemical shift value in the  $^1\text{H}$  NMR

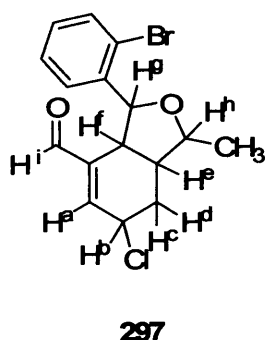


spectrum. Based on these facts the proposed structure for this aldehyde is as shown below in structure 297.



This structure was confirmed by the data obtained from the  $^1\text{H} - ^1\text{H}$  COSY experiment as shown in the following diagram.

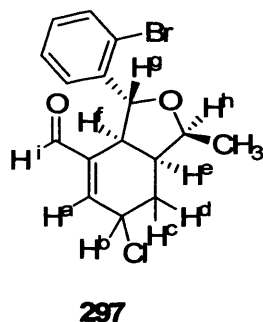
$^1\text{H} - ^1\text{H}$  COSY experiment showed the following correlations



$\text{H}^a$ ,  $\delta = 6.74$ , showed a cross peak to  $\text{H}^b$   
 $\text{H}^b$ ,  $\delta = 4.97 - 4.92$ , showed a cross peak to  $\text{H}^a$ ,  $\text{H}^f$  &  $\text{H}^d$   
 $\text{H}^f$  &  $\text{H}^d$ ,  $\delta = 2.20 - 2.14$ , showed a cross peak to  $\text{H}^b$  &  $\text{H}^e$   
 $\text{H}^e$ ,  $\delta = 2.59$ , showed a cross peak to  $\text{H}^f$ ,  $\text{H}^d$ ,  $\text{H}^f$  &  $\text{H}^i$   
 $\text{H}^f$ ,  $\delta = 3.23$ , showed a cross peak to  $\text{H}^b$  &  $\text{H}^e$   
 $\text{H}^d$ ,  $\delta = 5.04$ , showed a cross peak to  $\text{H}^f$   
 $\text{H}^i$ ,  $\delta = 4.72$ , showed a cross peak to  $\text{H}^e$  &  $\text{CH}_3$   
 $\text{CH}_3$ ,  $\delta = 1.27$ , showed a cross peak to  $\text{H}^i$

The relative stereochemistry of this product was identified as shown below based on the correlations obtained from the NOESY experiments. Unfortunately the stereochemistry at  $\text{H}^b$  could not be determined.

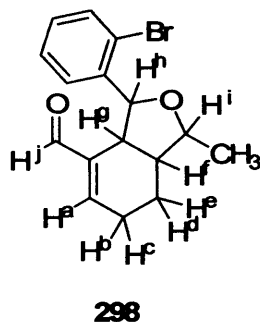
NOESY data for compound 297



$\text{H}^a$ ,  $\delta = 6.74$ , showed a cross peak to  $\text{H}^b$  &  $\text{H}^i$   
 $\text{H}^b$ ,  $\delta = 4.97 - 4.92$ , showed a cross peak to  $\text{H}^a$ ,  $\text{H}^f$  &  $\text{H}^d$   
 $\text{H}^f$  &  $\text{H}^d$ ,  $\delta = 2.20 - 2.14$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^e$ ,  $\text{H}^d$  &  $\text{CH}_3$   
 $\text{H}^e$ ,  $\delta = 2.59$ , showed a cross peak to  $\text{H}^f$  or  $\text{H}^d$  or both of them,  $\text{H}^f$  &  $\text{H}^i$   
 $\text{H}^f$ ,  $\delta = 3.23$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^e$  & aromatic H at  $\delta = 7.50$  ppm  
 $\text{H}^d$ ,  $\delta = 5.04$ , showed a cross peak to  $\text{H}^f$  or  $\text{H}^d$   
 $\text{H}^i$ ,  $\delta = 4.72$ , showed a cross peak to  $\text{H}^e$ ,  $\text{H}^f$  &  $\text{CH}_3$   
 $\text{H}^i$ ,  $\delta = 9.38$ , showed a cross peak to  $\text{H}^b$   
 $\text{CH}_3$ ,  $\delta = 1.27$ , showed a cross peak to  $\text{H}^i$   
 Aromatic H,  $\delta = 7.50$ , showed a cross peak to  $\text{H}^f$

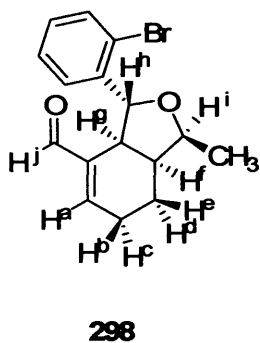
The second fraction eluted from the column was the major product in the crude reaction mixture and as indicated before it is an aldehyde without a chlorine atom, having very similar but different spectroscopic features to compound **288**.

$^1\text{H}$  -  $^1\text{H}$  COSY NMR spectroscopy showed the following correlations; confirming the connectivity. Therefore this compound is a stereoisomer of compound **288**.



$\text{H}^{\text{a}}$ ,  $\delta = 6.81$ , showed a cross peak to  $\text{H}^{\text{b}}$  &  $\text{H}^{\text{f}}$   
 $\text{H}^{\text{b}}$ ,  $\delta = 2.58$ , showed a cross peak to  $\text{H}^{\text{a}}$ ,  $\text{H}^{\text{c}}$ ,  $\text{H}^{\text{d}}$  &  $\text{H}^{\text{e}}$   
 $\text{H}^{\text{c}}$ ,  $\delta = 2.35 - 2.22$ , showed a cross peak to  $\text{H}^{\text{a}}$ ,  $\text{H}^{\text{b}}$ ,  $\text{H}^{\text{d}}$  &  $\text{H}^{\text{e}}$   
 $\text{H}^{\text{d}}$ ,  $\delta = 1.80$ , showed a cross peak to  $\text{H}^{\text{b}}$ ,  $\text{H}^{\text{c}}$ ,  $\text{H}^{\text{e}}$  &  $\text{H}^{\text{f}}$   
 $\text{H}^{\text{e}}$ ,  $\delta = 1.65$ , showed a cross peak to  $\text{H}^{\text{b}}$ ,  $\text{H}^{\text{c}}$ ,  $\text{H}^{\text{d}}$  &  $\text{H}^{\text{f}}$   
 $\text{H}^{\text{f}}$ ,  $\delta = 2.12$ , showed a cross peak to  $\text{H}^{\text{b}}$ ,  $\text{H}^{\text{c}}$ ,  $\text{H}^{\text{d}}$  &  $\text{H}^{\text{e}}$   
 $\text{H}^{\text{g}}$ ,  $\delta = 3.16$ , showed a cross peak to  $\text{H}^{\text{h}}$  &  $\text{H}^{\text{i}}$   
 $\text{H}^{\text{h}}$ ,  $\delta = 5.07$ , showed a cross peak to  $\text{H}^{\text{g}}$   
 $\text{H}^{\text{i}}$ ,  $\delta = 4.63$ , showed a cross peak to  $\text{H}^{\text{g}}$  &  $\text{CH}_3$   
 $\text{CH}_3$ ,  $\delta = 1.25$ , showed a cross peak to  $\text{H}^{\text{i}}$

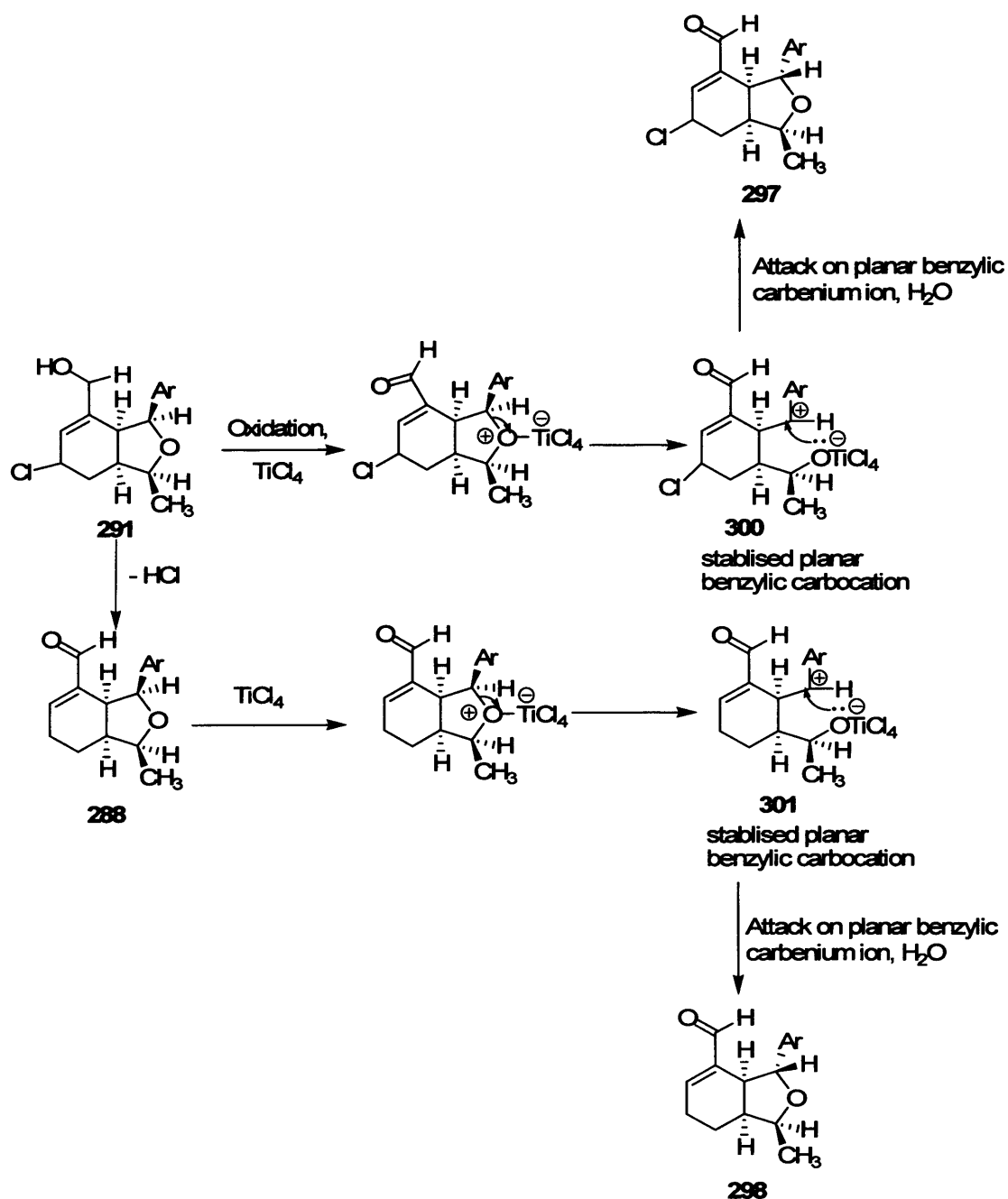
Then the relative stereochemistry in this product was identified as shown below based on the correlations obtained from the NOESY experiments



$\text{H}^{\text{a}}$ ,  $\delta = 6.81$ , showed a cross peak to  $\text{H}^{\text{b}}$ ,  $\text{H}^{\text{c}}$  &  $\text{H}^{\text{j}}$   
 $\text{H}^{\text{b}}$ ,  $\delta = 2.58$ , showed a cross peak to  $\text{H}^{\text{a}}$ ,  $\text{H}^{\text{c}}$ ,  $\text{H}^{\text{d}}$  &  $\text{H}^{\text{e}}$   
 $\text{H}^{\text{c}}$ ,  $\delta = 2.35 - 2.22$ , showed a cross peak to  $\text{H}^{\text{a}}$ ,  $\text{H}^{\text{b}}$ ,  $\text{H}^{\text{f}}$ ,  $\text{H}^{\text{d}}$  &  $\text{H}^{\text{e}}$   
 $\text{H}^{\text{d}}$ ,  $\delta = 1.80$ , showed a cross peak to  $\text{H}^{\text{b}}$ ,  $\text{H}^{\text{c}}$ ,  $\text{H}^{\text{f}}$ ,  $\text{H}^{\text{e}}$  &  $\text{CH}_3$   
 $\text{H}^{\text{e}}$ ,  $\delta = 1.65$ , showed a cross peak to  $\text{H}^{\text{b}}$ ,  $\text{H}^{\text{c}}$ ,  $\text{H}^{\text{f}}$ ,  $\text{H}^{\text{d}}$  &  $\text{CH}_3$   
 $\text{H}^{\text{f}}$ ,  $\delta = 2.12$ , showed a cross peak to  $\text{H}^{\text{b}}$ ,  $\text{H}^{\text{c}}$ ,  $\text{H}^{\text{d}}$ ,  $\text{H}^{\text{e}}$  &  $\text{CH}_3$   
 $\text{H}^{\text{g}}$ ,  $\delta = 3.16$ , showed a cross peak to aromatic H at  $\delta = 7.50$ ,  $\text{H}^{\text{h}}$ ,  $\text{H}^{\text{i}}$  &  $\text{H}^{\text{j}}$   
 $\text{H}^{\text{h}}$ ,  $\delta = 5.07$ , showed a cross peak to  $\text{H}^{\text{g}}$  &  $\text{H}^{\text{j}}$   
 $\text{H}^{\text{i}}$ ,  $\delta = 4.63$ , showed a cross peak to aromatic H at  $\delta = 7.50$ ,  $\text{H}^{\text{g}}$ ,  $\text{H}^{\text{f}}$  &  $\text{CH}_3$   
 $\text{H}^{\text{j}}$ ,  $\delta = 9.29$ , showed a cross peak to  $\text{H}^{\text{g}}$   
 $\text{CH}_3$ ,  $\delta = 1.25$ , showed a cross peak to  $\text{H}^{\text{i}}$ ,  $\text{H}^{\text{f}}$ ,  $\text{H}^{\text{d}}$  &  $\text{H}^{\text{e}}$

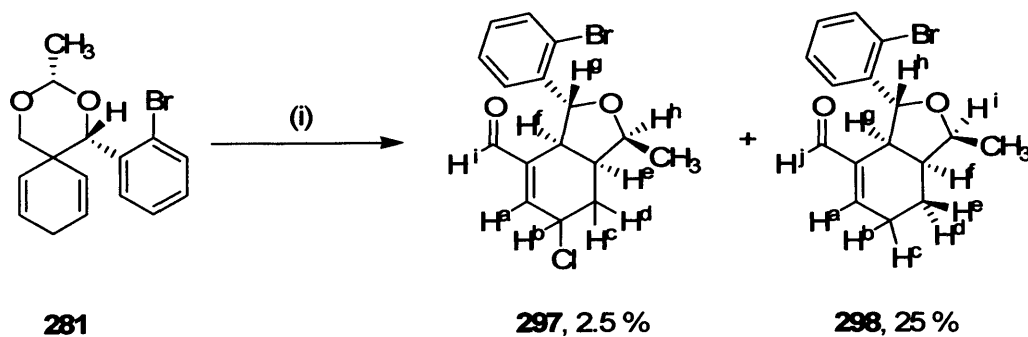
It is clear that compound **298** and compound **288** are epimers (they have different stereochemistry at the original stereogenic centre but have the same stereochemistry at the other three stereogenic centres). Also for compound **297** it has the same basic structure as compound **291** except for the alcohol group in compound **291** is replaced by an aldehyde group in compound **297**. Therefore with regard to the construction of the basic structure of both compounds **297** and **298**, it can be rationalised by the same mechanistic interpretation used for compounds **291** and **282**. However, with

regard to the stereochemistry issue, as indicated before the acceptable transition state model is conformer **293**, but this model resulted in the stereochemistry observed in compounds **291** and **288** which is opposite to both compounds **297** and **298** at the original stereogenic centre. Therefore initially it can be assumed that both compounds **297** and **298** were formed *via* conformer **293** that led to compound **291** followed by ring opening then recyclisation on the other double bond to give rise to the observed stereochemistry in compounds **297** and **298**. However, this pathway requires breaking of strong C-C bonds which is not reasonable under the reaction conditions. Alternatively, it can be proposed that both compounds **297** and **298** might be derived from compounds **291** and **288** respectively by epimerisation of the relatively acidic proton at the original stereogenic centre. This assumption is backed up by the fact that the epimerisation took place at the benzylic position to form a stabilised carbenium ion rather than at the position adjacent to the methyl group as shown in **Scheme 160**.



**Scheme 160**

Finally the outcome of the Lewis-acid catalysed Prins cyclisation of the acetaldehyde acetal **281** under the thermodynamic conditions can be summarised by the following **Scheme 161**.

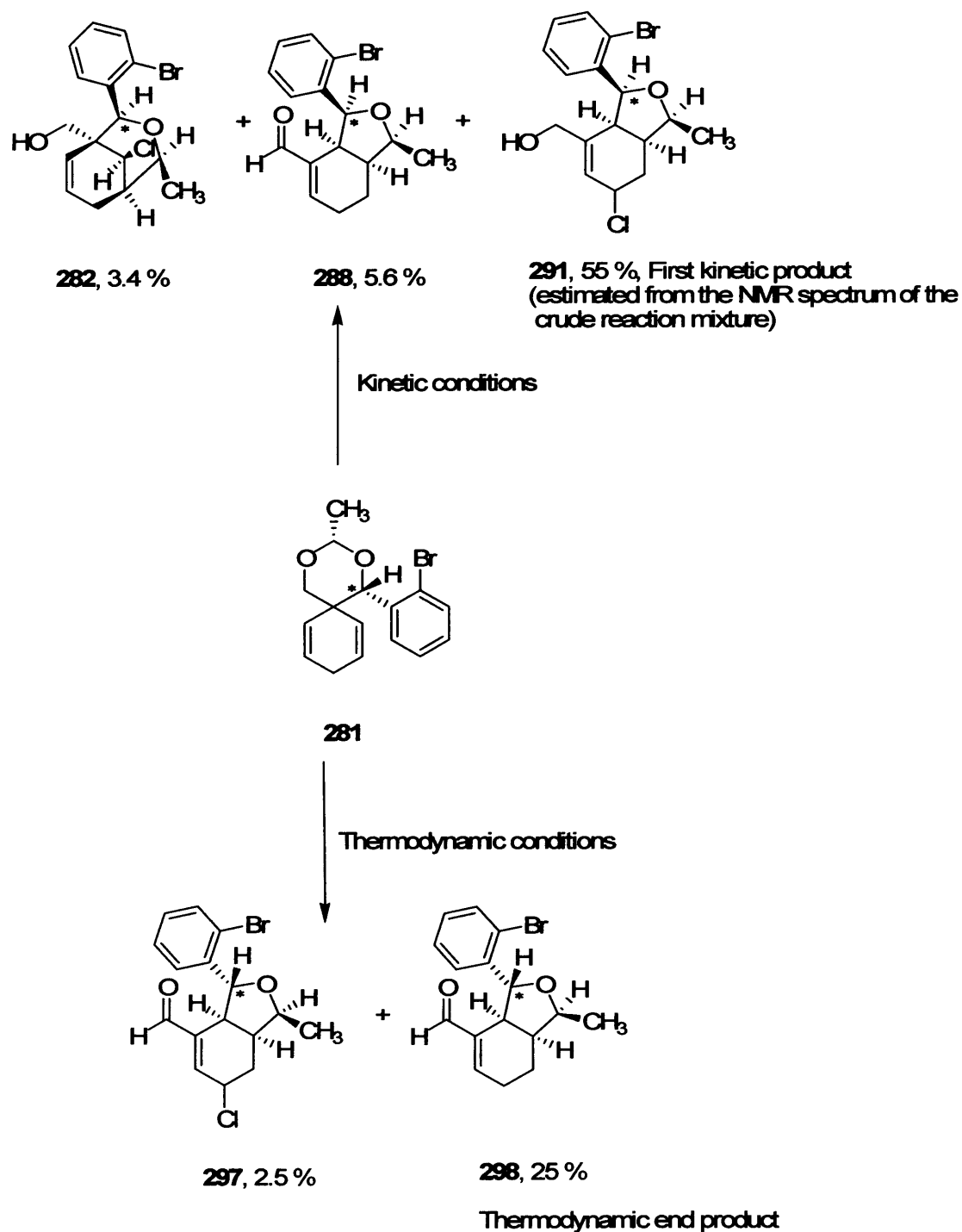


**Scheme 161** Reagents and conditions: (i)  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^\circ\text{C}$ , 1 h., r.t. 23 h.

To prove that compound **291** is the kinetic product of this reaction, the acetaldehyde acetal **281** was allowed to react with  $\text{TiCl}_4$  at  $-78\text{ }^\circ\text{C}$  for only ten minutes then the reaction mixture was worked up in a similar manner as before. This resulted in the formation of alcohol **291** essentially. The spectroscopic data obtained from this experiment was clear enough to identify compound **291** as shown above. This result is very important since it indicates that while alcohol **291** was being formed initially, it would likely be rearranged to the different obtained products.

So, the first Prins reaction of a cyclohexadiene derivative **281** was successful and it led to the formation of a range of different products (five products were identified; compounds **282**, **288**, **291**, **297**, and **298**) depending on the reaction conditions. All of the isolated products were tetrahydrofuran derivatives, except for compound **282** which is a tetrahydropyran derivative. Mechanistically, it can be assumed that all of these products were derived from a tetrahydropyranyl cation **286** that formed as a result of the favoured 6-*endo*-trig cyclisation on the right-hand side double-bond followed by a subsequent rearrangement except for compound **282** which was formed as a result of a subsequent nucleophilic capture of a chloride ion. In all of these products at least three new contiguous stereogenic centres were formed (in case of compound **282**, four new stereogenic centres were produced) with high level of stereocontrol under the influence of one stereochemical directing group. Two out of four of the isolated products particularly compound **282** and compound **288** which were formed under the kinetic conditions have all *cis* relationships at the newly formed rings. The other two compounds which were formed under the thermodynamic conditions have a *trans* relationship between all the newly formed stereogenic centres and the original stereogenic centre (the original stereogenic

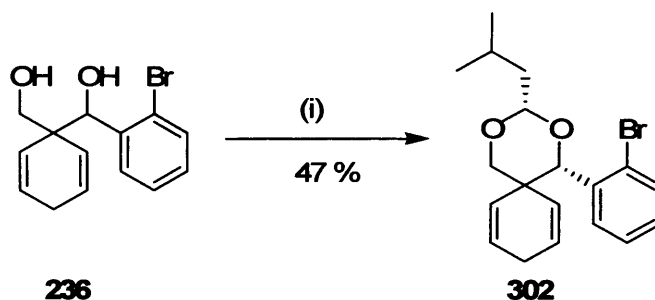
centre is indicated with asterisks in the structures shown below in **Scheme 162**. This may imply that the substituents could affect the outcome of the reaction.



**Scheme 162**

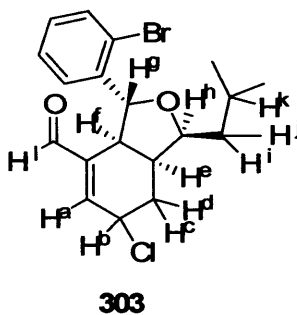
As indicated above, the relative stereochemistry of the original stereogenic centre and that of the newly formed ones could be varied. Therefore different substituents

will be needed to evaluate the scope and limitations of the Prins cyclisation reaction of cyclohexadiene derivatives. Thus the next suggestion was to increase the size of the alkyl group at the acetal centre. Therefore the diol **236** was protected as isovaleraldehyde acetal **302** which was formed a single diastereoisomer as shown in **Scheme 163**.



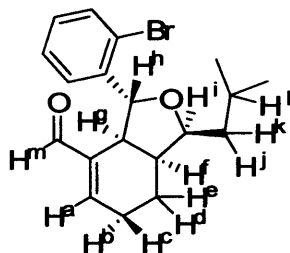
**Scheme 163** *Reagents and conditions:* (i) (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CHO, CH<sub>2</sub>Cl<sub>2</sub>, pyridinium *p*-toluenesulfonate, r.t., 4 days.

Treating of isobutyl acetal **302** with titanium tetrachloride under the thermodynamic conditions resulted in formation of two aldehydes; the major:minor ratio is approximately 1.4:1.0 as evident from the <sup>1</sup>H NMR spectrum of the crude reaction mixture. Purification by flash chromatography led to the isolation of these two products. The minor aldehyde **303** was the first to be eluted and it was identified as shown below. The assignment of this structure was based partly on the spectroscopic evidence and partly on the spectroscopic similarities with aldehyde **297**. Therefore the formation of compound **303** can be rationalised by the same the mechanistic interpretation used for compound **297**.



The key point in assigning this stereochemistry was the absence of any NOESY correlations between H<sup>g</sup> and H<sup>c</sup> or H<sup>h</sup>. However, the stereochemistry at H<sup>b</sup> could not be determined.

Then the major aldehyde was eluted and identified as shown in structure **304**. Similarly this structure was established by comparison of the spectroscopic data of the isolated fractions with those of aldehyde **298**.



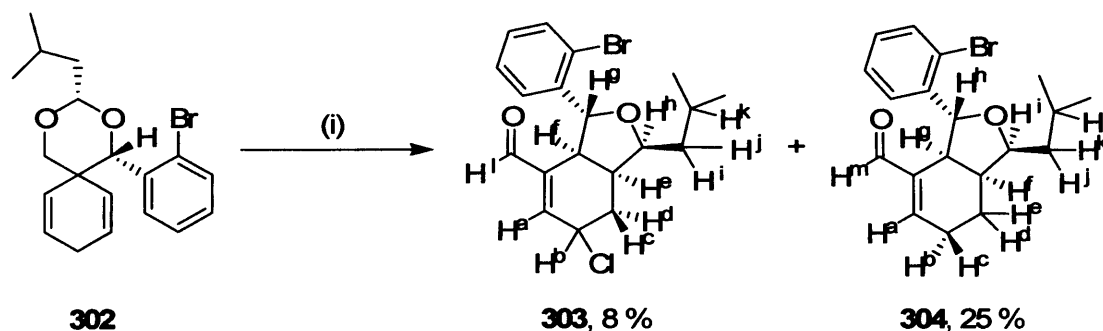
**304**

With respect to the observed stereochemistry of both compounds **303** and **304**, it fits with the results obtained in case of acetaldehyde acetal **281**. Therefore this stereochemistry is most likely to be due to epimerisation at the original stereogenic centre as explained before in **Scheme 160**.

While the product selection for this reaction was not great since the ratio of the two formed aldehydes in the crude reaction mixture was very close (1.4:1.0). On the other hand, the stereoselectivity was very good; only one isomer of each product was formed. Also in terms of the double bond selection both products seemed to be formed *via* electrophilic attack by the intermediate oxonium ion on the right-hand side double-bond as explained before in **Schemes 158, 159, and 160**.

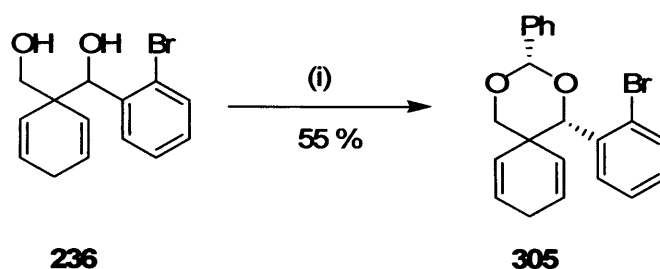
Therefore the outcome of the titanium-mediated cyclisation reaction of isobutyl acetal **302** under the thermodynamic conditions can be summarised as shown in **Scheme 164**.





**Scheme 164** *Reagents and conditions:* (i)  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^\circ\text{C}$ , 1 h., r.t., 14 h.

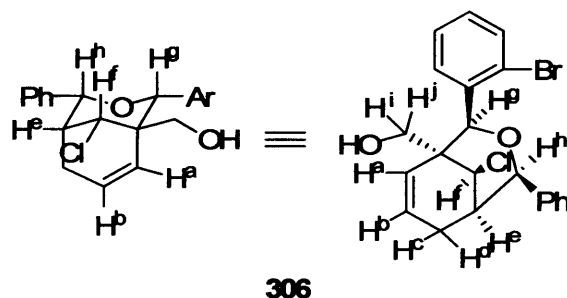
As can be seen from **Scheme 161** and **Scheme 164** the end products in the two attempted Prins cyclisation reactions under thermodynamic conditions have the same basic structure and the same stereochemistry. Also in both of these previous cases the substituent at the permanent homoallylic stereogenic centre was a 2-bromophenyl group while at the acetal centre which is destroyed during the course of the reaction the substituents were different alkyl groups (methyl and isobutyl). Therefore to test how general is the outcome of this type of reactions, first an aryl group is needed at the acetal centre. Also the situation when the permanent homoallylic stereogenic centre will have an alkyl group and the acetal centre will have different alkyl and aryl groups needs to be investigated. Thus, firstly treating a solution of diol **236** in DMF with benzaldehyde and sulphuric acid delivered the requisite cyclisation precursor **305** as a single diastereoisomer (**Scheme 165**).



**Scheme 165** *Reagents and conditions:* (i)  $\text{PhCHO}$ ,  $\text{H}_2\text{SO}_4$ , DMF, r.t. 6 days

Subjecting benzaldehyde acetal **305** to the standard thermodynamic conditions resulted in the formation of aromatic decomposition products. On the other hand, treating the same substrate with titanium tetrachloride at  $-78\text{ }^\circ\text{C}$  for only two hours resulted in the formation of a mixture of three compounds (major, minor and very

minor) in 5.2:2.8:1.0. Purification of the crude reaction mixture by flash chromatography resulted in the isolation of these compounds. The first compound to be eluted from the column was identified as the minor in the crude reaction mixture. Initially, the  $^1\text{H}$  NMR spectrum of this compound revealed the following information. There were two alkene protons. There was no aldehyde proton but two diastereotopic  $\text{CH}_2$  protons were evident. Therefore this compound is an unrearranged alcohol. Also the  $^{13}\text{C}$  NMR spectrum revealed the presence of three aliphatic CH groups attached to heteroatoms (O, Cl). Based on these observations and the data obtained previously, this compound is the result of the favoured 6-*endo*-trig cyclisation followed by nucleophilic capture of a chloride ion. Therefore the assumed structure is as shown below.

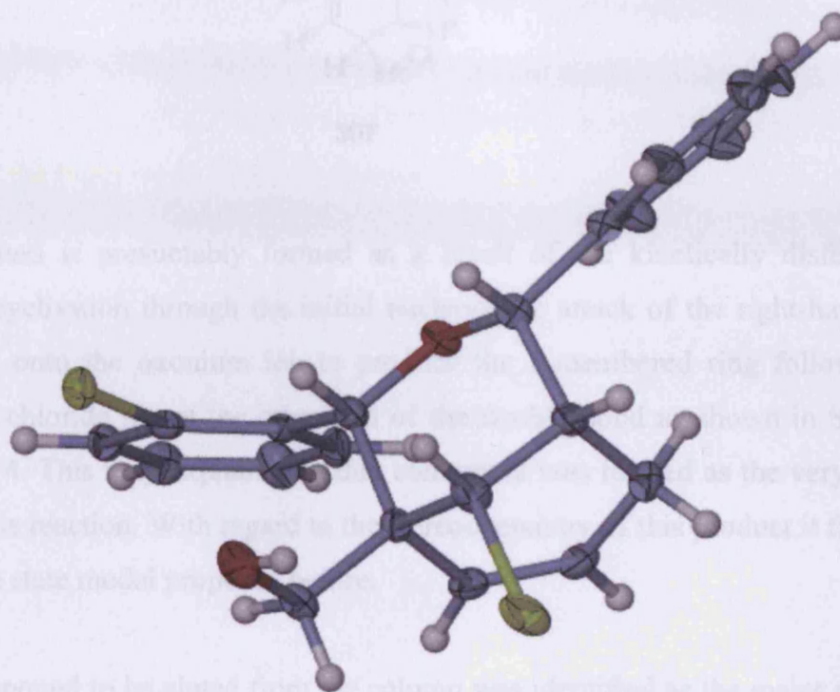


The  $^1\text{H}$  NMR spectrum of this compound showed that  $\text{H}^h$  and  $\text{H}^f$  were overlapped and they gave one broad resonance peak although both of them couple to the same ring junction proton  $\text{H}^e$  as appeared from the  $^1\text{H} - ^1\text{H}$  COSY experiment so it was expected they would each give a doublet peak.

To clarify this observation by proving that these two overlapped protons were indeed  $\text{H}^h$  and  $\text{H}^f$ , the  $^1\text{H} - ^{13}\text{C}$  correlation experiment was run and it showed that the peak at  $\delta = 4.92$  ppm in the  $^1\text{H}$  NMR spectrum which corresponds to the two overlapped protons also correspond to two downfield CH groups at  $\delta = 80.9$  ppm and  $62.7$  ppm in the  $^{13}\text{C}$  NMR spectrum. These high chemical shift values indicated that these two carbons correspond to carbons attached to hetero atoms. Therefore it proved that the previous assignment was correct.

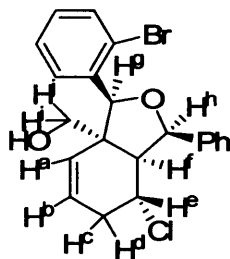
Moreover, the data obtained from the NOESY experiment were slightly ambiguous due to the overlap between these two protons ( $\text{H}^h$  and  $\text{H}^f$ ) and the proximity of  $\text{H}^a$  which made it was difficult to prove the stereochemistry. But fortunately this

compound crystallised readily and its X-ray spectroscopic data allowed us to confirm the structure and the stereochemistry to be as shown in **Figure 11**.



**Figure 11** Structure of compound **306** from X- ray data.

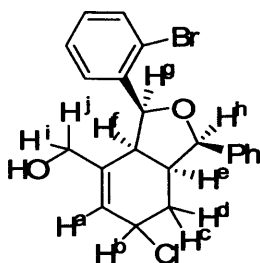
The second compound to be eluted from the column was the very minor compound in the crude reaction mixture (although it was isolated in higher yield than the minor compound after the flash chromatography). Similarly, this compound is unrearranged alcohol and its structure including the stereochemistry was determined through the data obtained from the  $^1\text{H}$ ,  $^{13}\text{C}$  NMR,  $^1\text{H}$  -  $^1\text{H}$  COSY experiment, NOESY experiment, and  $^1\text{H}$  -  $^{13}\text{C}$  correlation spectra. Although it was impossible to prove the stereochemistry conclusively due to the closeness of  $\text{H}^g$  and  $\text{H}^h$ , it was most likely to be as shown in the diagram below. Also the stereochemistry of  $\text{H}^e$  was assigned as shown based on the fact that there was no cross peak between it and the adjacent  $\text{H}^f$ .



**307**

This compound is presumably formed as a result of the kinetically disfavoured 5-*endo*-trig cyclisation through the initial nucleophilic attack of the right-hand side double-bond onto the oxonium ion to produce the 5-membered ring followed by capture of a chloride ion at the other end of the double bond as shown in **Scheme 149**, page 114. This may explain why that compound was formed as the very minor product in this reaction. With regard to the stereochemistry of this product it fits with the transition state model proposed before.

The last compound to be eluted from the column was identified as the major product in the crude reaction mixture. Apparently this compound is the most stable product. This compound has only one alkene CH group; therefore it is a rearrangement product. The structure of this compound was established based on the data obtained from  $^1\text{H}$ ,  $^{13}\text{C}$  NMR spectra and  $^1\text{H}$  -  $^1\text{H}$  COSY experiments. Again although definite assignment for the stereochemistry was impossible due to the closeness in the chemical shift values of  $\text{H}^b$  and  $\text{H}^e$  and the overlap between  $\text{H}^c$  and  $\text{H}^d$ , the relative stereochemistry in this compound is most likely to be as shown below.

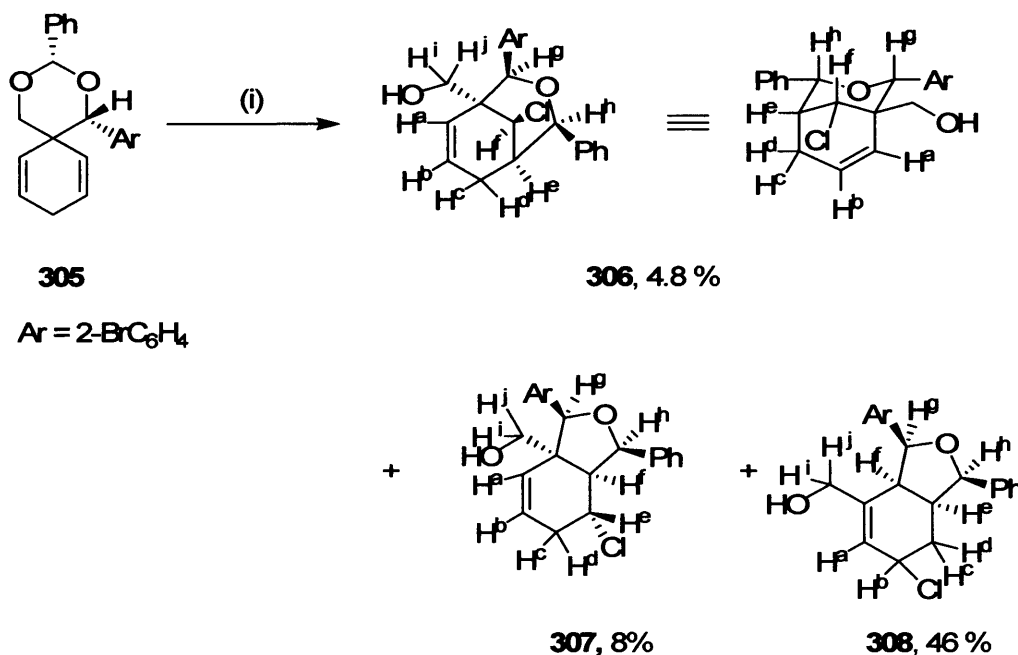


**308**

This result is consistent with the data obtained with acetaldehyde acetal **281**. Interestingly, this compound has the same basic structure and the same

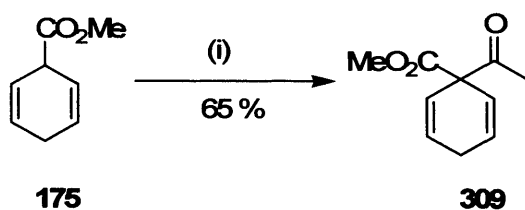
stereochemistry as compound **291** (the major product in the reaction of acetaldehyde acetal **281** under the same conditions) which was not isolated from the reaction. It seemed that replacing the methyl group in the acetal stereogenic centre by a phenyl group enhanced the stability of the product under the kinetic conditions.

Finally, the attempted Prins cyclisation of benzaldehyde acetal **305** and the obtained yields can be summarised as shown in **Scheme 166**.



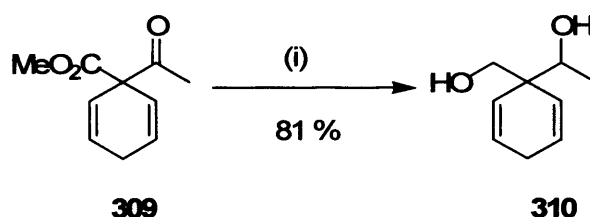
**Scheme 166** *Reagents and conditions:* (i)  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 2 h.

The next objective was examining the diastereoselective Prins cyclisation of acetal substrates derived from a cyclohexadiene having an alkyl group at the permanent homoallylic stereogenic centre on the acetal ring and different alkyl and aryl substituents at the acetal stereogenic centre. Thus treatment of the lithium enolate derived from ester **175** with acetyl chloride afforded ketoester **309** in 65 % yield.



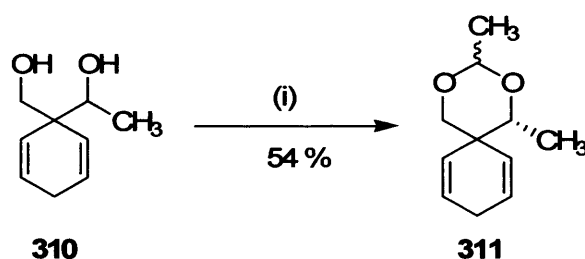
**Scheme 167** *Reagents and conditions:* (i)  $i\text{-Pr}_2\text{NH}$ ,  $n\text{-BuLi}$ , THF,  $-78^\circ\text{C}$ , 30 min, **175**, 30 min.,  $\text{CH}_3\text{COCl}$ , 1 h, then r.t., 18 h.

Reduction of ketoester **309** with  $\text{LiAlH}_4$  afforded diol **310** in 81 % yield (**Scheme 168**).



**Scheme 168 Reagents and Conditions:** (i)  $\text{LiAlH}_4$ , THF, r.t., 18 h., 15 % NaOH,  $\text{H}_2\text{O}$ , r.t., 2 h.

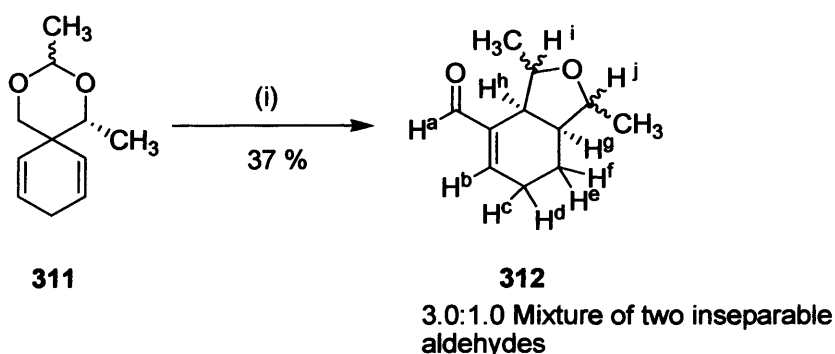
Protection of diol **310** as the acetaldehyde acetal **311** afforded the substrate for the titanium tetrachloride-promoted Prins cyclisation in 54 % yield as a mixture of two diastereoisomers (**Scheme 169**).



**Scheme 169 Reagents and conditions:** (i)  $\text{MeCHO}$ ,  $\text{CH}_2\text{Cl}_2$ , pyridinium *p*-toluenesulfonate, r.t., 6 days.

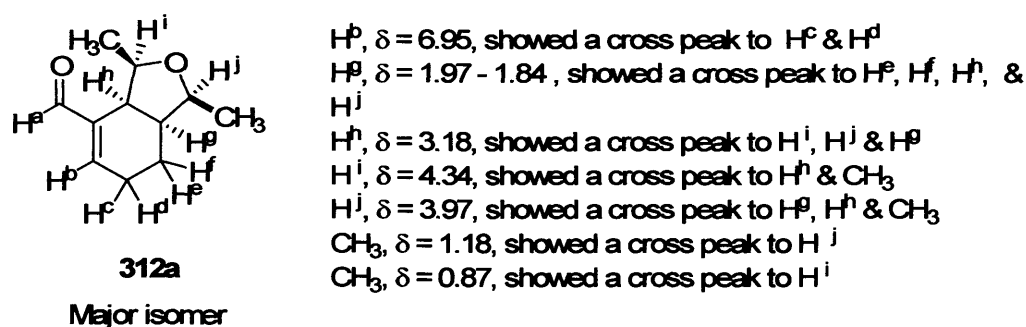
Treating acetaldehyde acetal **311** with titanium tetrachloride under the thermodynamic conditions resulted in a clean reaction. The  $^1\text{H}$  NMR spectrum of the crude reaction mixture revealed the presence of two aldehydes in a major:minor ratio of 3.0:1. Attempting to separate these two aldehydes by flash chromatography did not work. However, it was obvious that they have the same basic structure since they have the same spectroscopic features as revealed from the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the purified mixture. Therefore it was assumed that they are stereoisomers. Initially, the  $^{13}\text{C}$  NMR spectrum of the purified mixture revealed the following information. There was one aldehyde CH group and one alkene CH group for each isomer. There was a deshielded quaternary carbon for each isomer which corresponds to the  $\alpha$ -alkene carbon. There were four aliphatic CH groups for each

isomer; two of them are at higher chemical shift values corresponding to the two CH groups attached to the oxygen atom of the tetrahydrofuran ring. The remaining two correspond to the ring junction CH groups. There were two CH<sub>2</sub> groups for each isomer. All of these data imply that these two aldehydes lack the chlorine atom. Finally, assigning the structure was accomplished by comparing the data of this mixture with those of the previous reactions and was confirmed by the other spectroscopic data including <sup>1</sup>H - <sup>1</sup>H COSY experiments as shown in **Scheme 170**.



**Scheme 170** Reagents and conditions: (i) TiCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 1 h., r.t., 23 h.

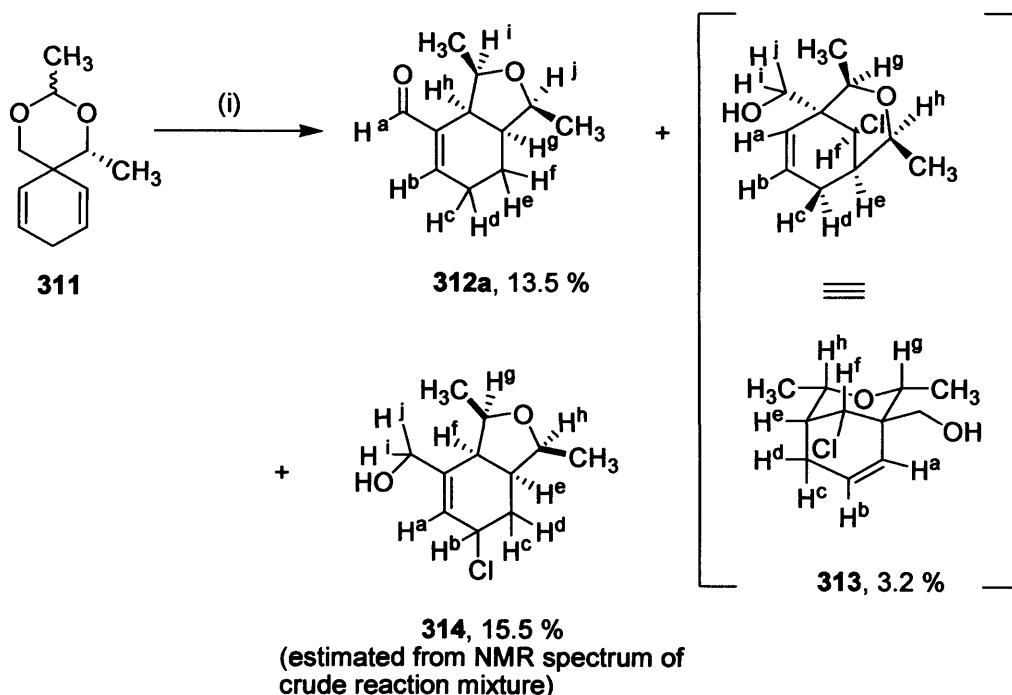
The major isomer showed the following cross peaks in the NOESY experiment, run on the mixture of the two isomers.



We have previously seen that the presence of an NOE between H<sup>h</sup> and H<sup>i</sup> does not prove that these hydrogen atoms are on the same side of the ring. From the results of the previous two reactions carried out under similar conditions (**Scheme 161** and **Scheme 164**) the major isomer had the stereochemistry of the newly formed three stereogenic centres opposite to that of the original homoallylic stereogenic centre. We believe that this results from an epimerisation after the Prins reaction as already

discussed. Since only the benzylic CH is epimerised, it is reasonable to assume that the corresponding stereogenic centre in compound **312a** above is as shown, with no epimerisation. We have additional evidence which supports this assignment as described below.

The stereochemistry of the minor isomer **312b** cannot be deduced from the NOESY spectrum of the mixture. In order to propose a structure for this compound, we need to discuss the results of the Prins reaction of compound **311** under kinetic conditions. When compound **311** was reacted under the kinetic conditions, three products were evident in the  $^1\text{H}$  NMR spectrum of the crude reaction mixture. Only one of these products was an aldehyde, and this was found to be identical to aldehyde **312a** formed under the thermodynamic conditions. There was none of the minor aldehyde **312b** formed under the kinetic conditions, so it seems unlikely that compound **312b** is formed by attack on the other double bond (since we would expect the formation and initial reaction of the oxonium to be complete within an hour, and the kinetic and thermodynamic conditions are identical up to this point). The other products are as shown in **Scheme 171**, although the chloroalcohol, with presumed stereochemistry as shown (**314**) was not isolated (as before).

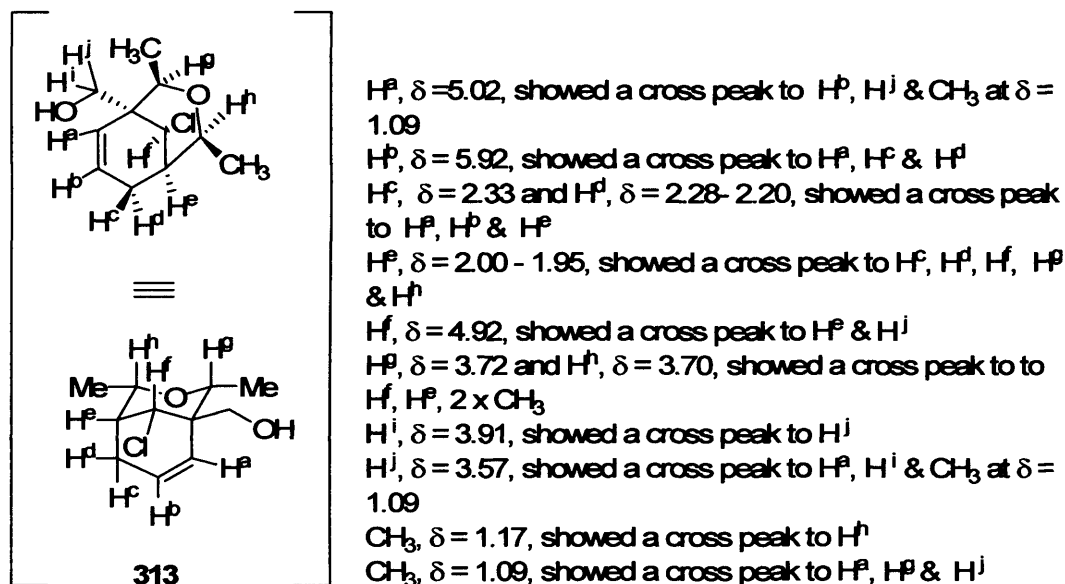


**Scheme 171** Reagents and conditions: (i)  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 2 h.

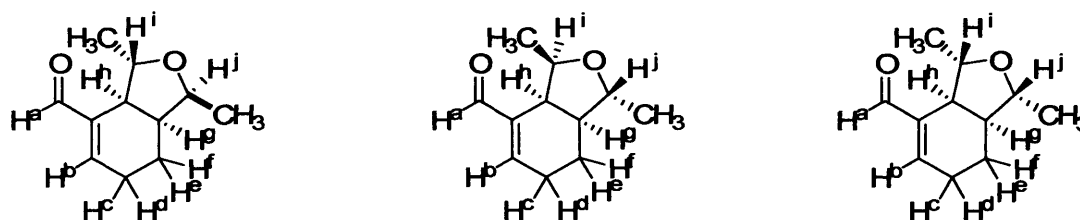


The ratio of compounds **314**:**313**:**312a** from the  $^1\text{H}$  NMR spectrum of the crude reaction mixture was 4.4:2.8:1.0. The assignment of the stereochemistry of aldehyde **312a** has been described above. The fact that this is the only isomer formed under the kinetic conditions supports this assignment. The tetrahydropyran **313** was assigned based on NOESY data as shown below.

NOESY experiment showed the following correlations

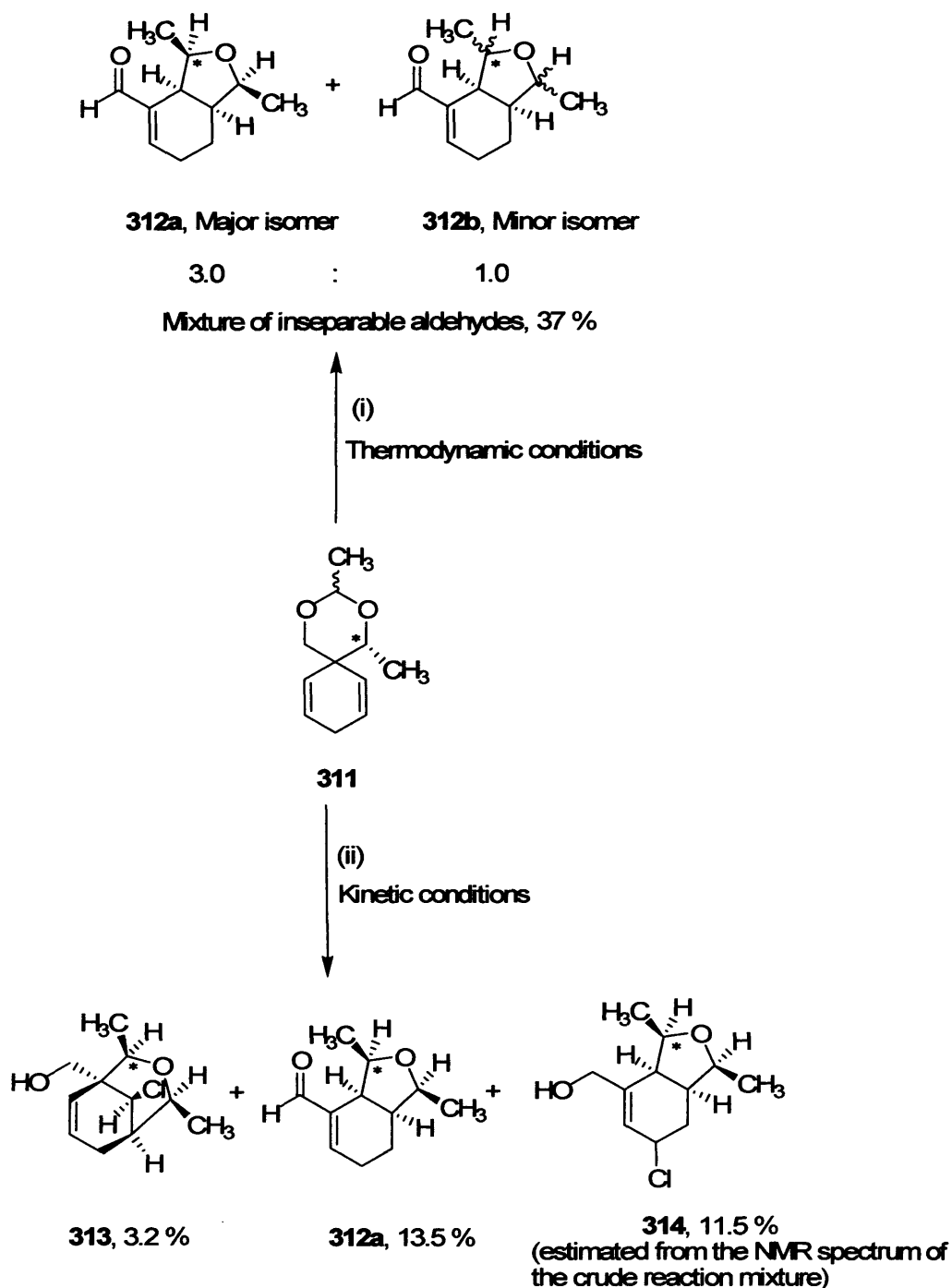


All of the compounds identified under kinetic and thermodynamic conditions arose from attack at the same double-bond. This is consistent with the mechanistic model described above (page 126). It seems likely that the minor aldehyde **312b** from the thermodynamic reaction conditions is formed by epimerisation of the major aldehyde **312a**, so that this compound is likely to have one of the three structures shown in **Figure 12**. We do not have data which will allow us to distinguish between these possibilities.



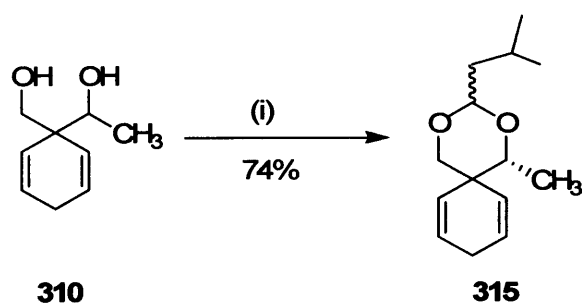
**Figure 12.** Possible stereochemical structures for aldehyde **312b**

These two reactions are therefore highly stereoselective with respect to the double-bond attacked, and can be summarised as shown in **Scheme 172**.



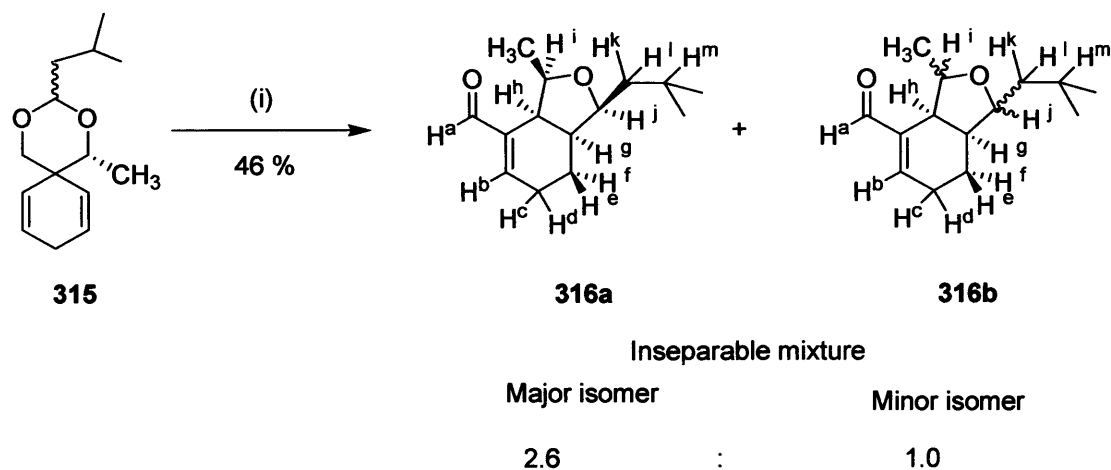
**Scheme 172** *Reagents and conditions:* (i)  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^\circ\text{C}$ , 1 h., r.t., 23 h.; (ii)  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^\circ\text{C}$ , 2 h.

The next substrate to be examined was isobutyl acetal **315** which was prepared as a mixture of two diastereoisomers by reaction of diol **310** with 3-methylbutyraldehyde as shown in **Scheme 173**.



**Scheme 173** *Reagents and conditions:* (i)  $(\text{CH}_3)_2\text{CHCH}_2\text{CHO}$ ,  $\text{CH}_2\text{Cl}_2$ , pyridinium *p*-toluenesulfonate, r.t., 9 days.

Subjecting isobutyl acetal **315** to the standard thermodynamic cyclisation conditions again resulted in a mixture of two inseparable aldehydes having the same spectroscopic features (stereoisomers) in a major: minor ratio of 2.6:1.0. The structure of these aldehydes was established from their spectroscopic data including  $^1\text{H}$  and  $^{13}\text{C}$  NMR,  $^1\text{H} - ^1\text{H}$  COSY and NOESY experiments as shown in **Scheme 174**.

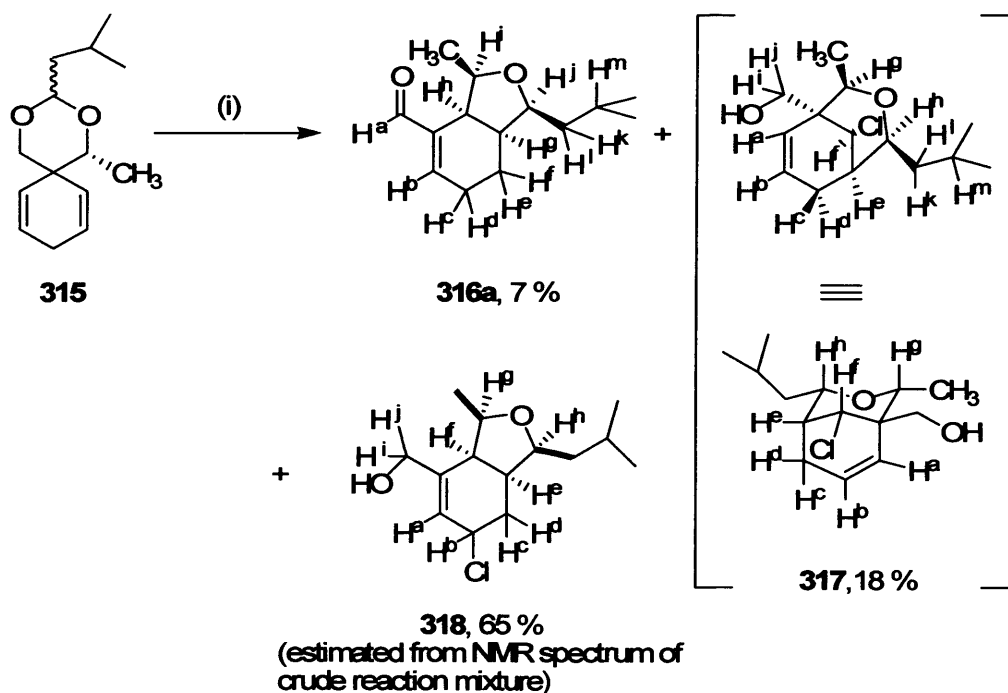


**Scheme 174** *Reagents and conditions:* (i)  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 1 h., r.t., 23 h.

Assignment of the stereochemistry of the major isomer was difficult. In the NOESY data, a cross peak was observed between  $\text{H}^i$  and  $\text{H}^h$ , although as we have seen, this is not an indication of stereochemistry. As the spectra of compound **316** were very similar to those of the previous compound **312**, we propose that they have identical stereochemistry. As above (**Figure 12**), we have three stereochemical possibilities

for the structure of compound **316b**. These could not be distinguished with the available data, and are not shown.

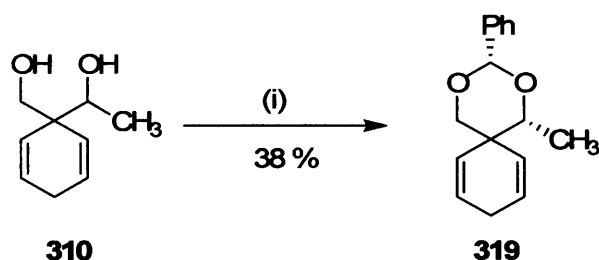
The reaction of compound **315** under the kinetic conditions gave essentially the same result as that obtained with compound **311**. This result therefore reinforces the conclusions drawn above. The results of this reaction are shown in **Scheme 175**.



**Scheme 175** Reagents and conditions: (i)  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^\circ\text{C}$ , 2 h.

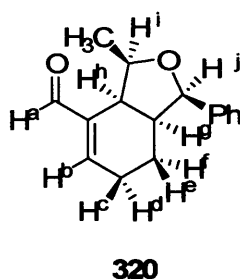
The ratio of compounds **316a**:**317**:**318** from the  $^1\text{H}$  NMR spectrum of the crude reaction mixture was 1.0:2.1:4.2. Only compounds **316a** and **317** were isolated in pure form, and were characterised by a range of techniques, including NOESY NMR. The data support the stereochemical assignments shown.

The last substrate to be examined to evaluate the effect of the substituents on the outcome of the Prins cyclisation of cyclohexadiene derivatives was compound **319**. This compound was prepared by reaction of diol **310** with benzaldehyde as a single diastereoisomer (**Scheme 176**).

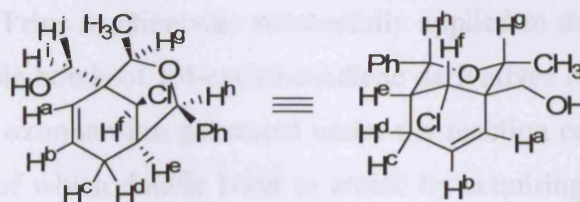


**Scheme 176** *Reagents and conditions:* (i) PhCHO, H<sub>2</sub>SO<sub>4</sub>, DMF, r.t. 7 days.

Subsequent treatment of benzaldehyde acetal **319** with titanium tetrachloride under the standard thermodynamic conditions resulted in the formation of aromatic decomposition products. Therefore the reaction was repeated under milder conditions by stirring the reaction mixture at -78 °C for two hours. In this case the reaction resulted in the formation of mainly two compounds in a major:minor ratio of 3.4:1.0. The major compound in the crude reaction mixture was identified as an unrearranged alcohol as indicated by the presence of two alkene protons and two diastereotopic protons having chemical shift value consistent with protons next to an oxygen atom. The minor compound was identified as an aldehyde which does not have a chlorine atom as evident by the presence of an aldehyde proton and two CH<sub>2</sub> groups respectively. These two compounds were separated by flash column chromatography. The aldehyde was eluted first and its structure was established by analysis of the spectroscopic data of the isolated fractions including <sup>1</sup>H, <sup>13</sup>C NMR, <sup>1</sup>H – <sup>1</sup>H COSY, and NOESY experiments. These data were very similar to the data obtained under the same reaction conditions using different substrates which confirmed the structure as shown below.

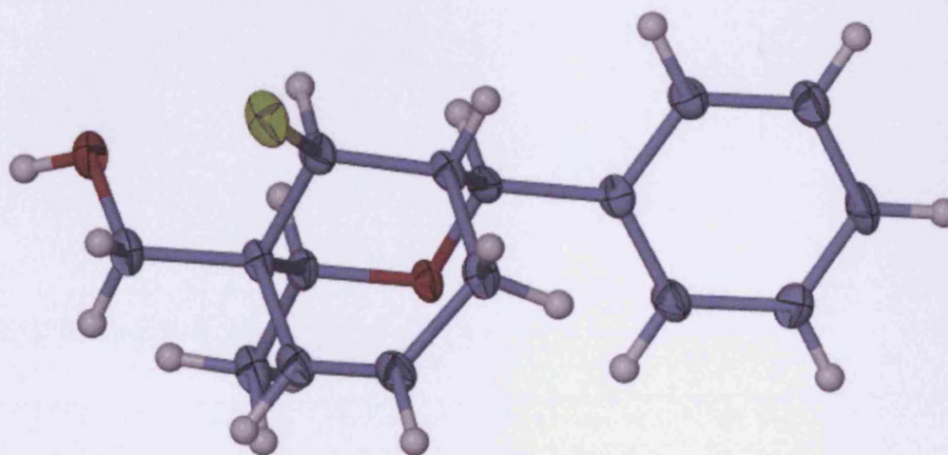


Then the major compound was eluted from the column and its structure including the stereochemistry was established from the spectroscopic data of the isolated fractions including <sup>1</sup>H, <sup>13</sup>C NMR, <sup>1</sup>H – <sup>1</sup>H COSY, and NOESY experiments as shown below.



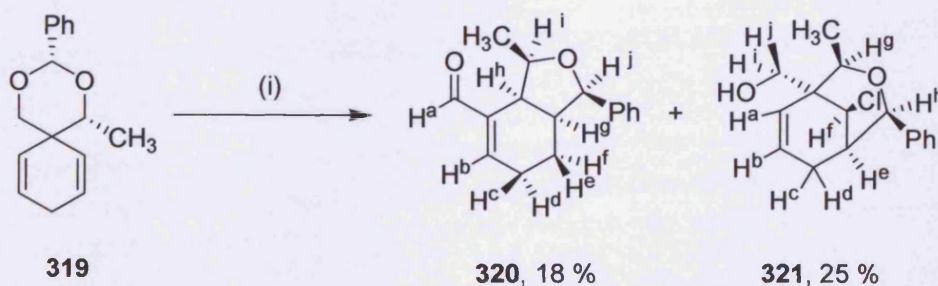
321

Fortunately, this compound gave suitable crystals for an X-ray analysis; this proved the relative configuration as shown in **Figure 13**.



**Figure 13** Structure of compound **321** from X-ray data.

Therefore the overall Prins cyclisation of benzaldehyde acetal **319** can be summarised as shown in **Scheme 177**.



**Scheme 177** Reagents and conditions: (i)  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 2 h.

To summarise, the Prins reaction was successfully applied to desymmetrise the two diastereotopic double bonds of 1,4-cyclohexadiene derivatives for the first time. The intermediate chiral oxonium ion generated under the reaction conditions was highly selective in terms of which double bond to attack by acquiring the more stabilised trans conformer to avoid the A<sup>1,3</sup> destabilising interactions between the substituents in the other conformers.

The stereochemistry of all products isolated can be explained by conformer **293** on **Scheme 158**, page 126. However, under thermodynamic conditions one (or possibly more) stereogenic centres undergo epimerisation.

## **Chapter 6**

### **Experimental Section**

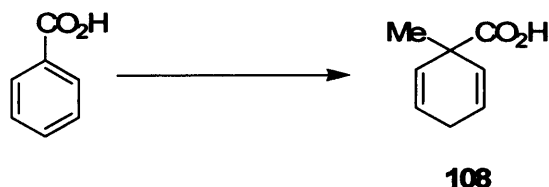


### 6.1. General Experimental Points

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a Fisons VG Platform II spectrometer and on a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for  $^1\text{H}$  and at 100 MHz for  $^{13}\text{C}$  at 25 °C, or on a Bruker Avance 500 spectrometer operating at 500 MHz for  $^1\text{H}$  and 125 MHz for  $^{13}\text{C}$  at 25 °C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants ( $J$ ) are reported in Hz. Multiplicity in  $^1\text{H}$ -NMR is reported as singlet (s), doublet (d), double doublet (dd), double triplet (dt), double quartet (dq), triplet (t), and multiplet (m). Multiplicity in  $^{13}\text{C}$ -NMR was obtained using the DEPT pulse sequence. Flash chromatography was performed using Matrex silica 60 35-70 micron.

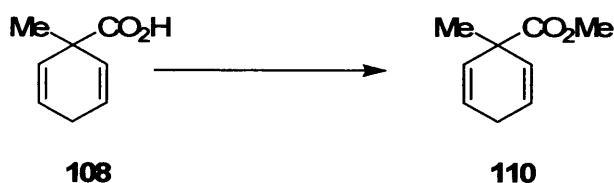
## 6.2. Experimental Data for Chapter 2

### 1-Methyl-cyclohexa-2,5-dienecarboxylic acid (**108**)<sup>31</sup>



Ammonia (500 cm<sup>3</sup>) was added to benzoic acid (10 g, 82 mmol) in a 1 l round bottomed flask through a dry ice-acetone condenser. With careful stirring, Li (1.6 g, 230 mmol) was added portion-wise until a permanent blue colour persisted. After 15 min at this temperature, iodomethane (14.6 ml, 234 mmol) was added slowly over a period of 5 min. The ammonia was allowed to evaporate overnight and the residue was dissolved in iced water. Dilute H<sub>2</sub>SO<sub>4</sub> was added until pH 1 - 2 was reached. The solution was then extracted into diethyl ether (3 × 200 ml). The combined ethereal extracts were dried over MgSO<sub>4</sub>. After removal of the solvent, the resulting pale brown oil solidified upon cooling. The resulting solid was recrystallised from light petroleum to give the *title acid* (9.8 g, 86 %) as a golden solid, m.p. 32 - 34 °C (lit. m.p. 36 °C);  $\nu_{\text{max}}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3500 – 2500 (broad), 2922, 2848, 1704, 1459, 1377, 1294, 1126, 942;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 5.78 (2 H, app. dt, *J* 10.4, 3.0, 2 × CH=CH-CH<sub>2</sub>), 5.70 (2 H, app. dt, *J* 10.4, 1.6, 2 × CH=CH-CH<sub>2</sub>), 2.61 - 2.56 (2 H, m, ring CH<sub>2</sub>), 1.29 (3 H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 181.9 (C=O), 128.0 (2 × alkene CH), 125.0 (2 × alkene CH), 43.7 (C<sub>q</sub> ring), 27.2 (CH<sub>3</sub>), 25.9 (ring CH<sub>2</sub>).

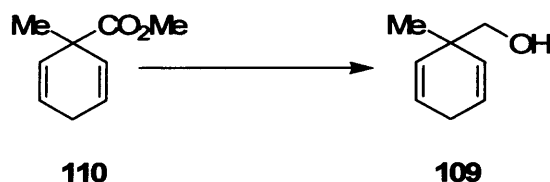
### 1-Methyl-cyclohexa-2,5-dienecarboxylic acid methyl ester (**110**)<sup>34</sup>



1-Methyl-cyclohexa-2,5-dienecarboxylic acid **108** (7.9 g, 57.2 mmol) was dissolved in absolute methanol (80 ml) and conc. H<sub>2</sub>SO<sub>4</sub> (0.18 ml) was added. After refluxing the reaction mixture for 6 h, most of the solvent was evaporated. The remaining

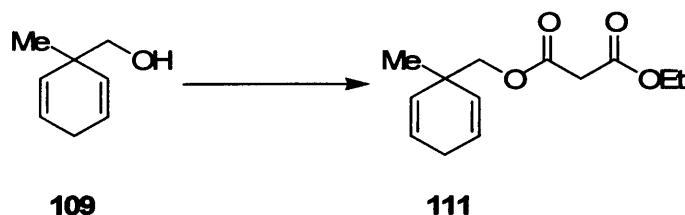
solution was neutralised by addition of saturated NaHCO<sub>3</sub> solution. The organic product was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 ml), dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford the *title ester* (8.2 g, 80 %) as an essentially-pure pale oil which was used without further purification;  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3032, 2930, 1728, 1454, 1248, 1110, 889, 706;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 5.80 (2 H, app. dt, *J* 10.5, 2.9, 2 × CH=CH-CH<sub>2</sub>), 5.75 (2 H, app. dt, *J* 10.5, 1.7, 2 × CH=CH-CH<sub>2</sub>), 3.67 (3 H, s, O-CH<sub>3</sub>), 2.71 - 2.56 (2 H, m, ring CH<sub>2</sub>), 1.32 (3 H, s, C<sub>q</sub>-CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 175.7 (C=O), 128.6 (2 × alkene CH), 124.4 (2 × alkene CH), 52.2 (O-CH<sub>3</sub>), 43.8 (C<sub>q</sub> ring), 27.4 (C<sub>q</sub>-CH<sub>3</sub>), 25.8 (ring CH<sub>2</sub>).

**(1-Methyl-cyclohexa-2,5-dienyl)-methanol (109)**<sup>32b,34</sup>



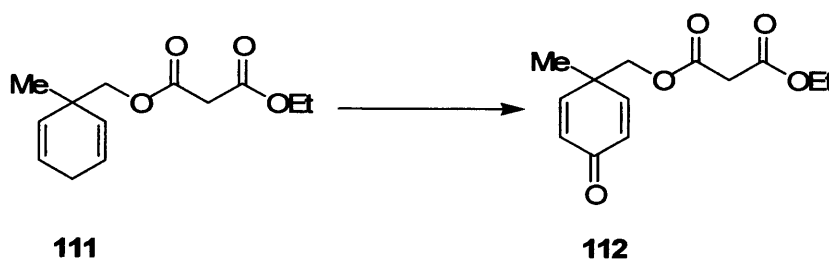
To a stirred suspension of LiAlH<sub>4</sub> (1.79 g, 47.7 mmol) in dry THF (40 ml) under a nitrogen atmosphere at room temperature was added a solution of ester **110** (5 g, 32.9 mmol) in dry THF (8 ml). The mixture was stirred at room temperature for 7 hours, then 15 % aqueous NaOH solution (1.7 ml) was added carefully followed by water (5.5 ml) and stirring was continued at room temperature for 17 hours. Filtration and concentration under reduced pressure afforded the *title alcohol* **109** (3.7 g, 91 %) as a pale yellow oil which used without further purification;  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3367, 3006, 2946, 2865, 1635, 1456, 1422, 1037, 715;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 5.78 (2 H, app. dt, *J* 10.4, 3.4, 2 × CH=CH-CH<sub>2</sub>), 5.33 (2 H, app. dt, *J* 10.4, 2.0, 2 × CH=CH-CH<sub>2</sub>), 3.19 (2 H, d, *J* 6.1 CH<sub>2</sub>-OH), 2.64 - 2.44 (2 H, m, ring CH<sub>2</sub>), 1.32 (1 H, t, *J* 6.1, OH), 0.88 (3 H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 131.2 (2 × alkene CH), 125.7 (2 × alkene CH), 70.8 (OCH<sub>2</sub>), 38.9 (C<sub>q</sub> ring), 26.4 (ring CH<sub>2</sub>), 24.8 (CH<sub>3</sub>).

**Malonic acid ethyl ester 1-methyl-cyclohexa-2,5-dienylmethyl ester (111)**



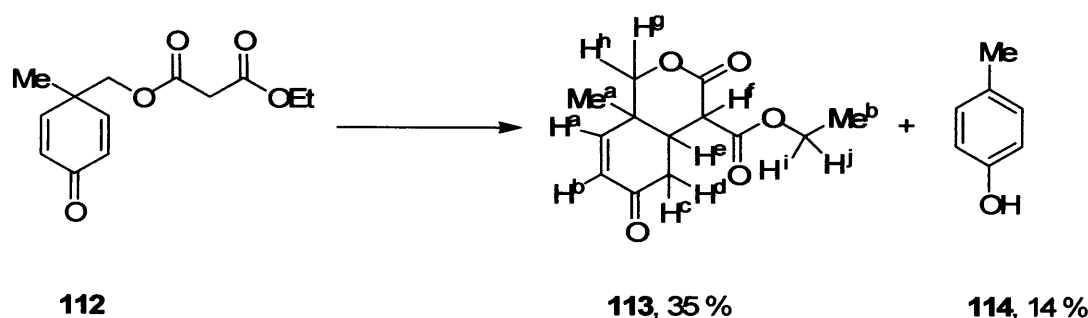
Ethyl malonyl chloride (1.5 g, 1.3 ml, 9.9 mmol, 1.1 equiv.) dissolved in dry  $\text{CH}_2\text{Cl}_2$  (5 ml) was added to a solution of the alcohol **109** (1.1 g, 8.9 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (45 ml). Triethylamine (0.99 g, 1.4 ml, 9.8 mmol, 1.1 equiv.) and DMAP (few crystals) were added. After stirring the resulting mixture at room temperature for 24 hours, aqueous 2 M HCl solution (20 ml) was added and the organic material was extracted into  $\text{CH}_2\text{Cl}_2$  (3  $\times$  30 ml). The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to afford a brown oil. The resulting oil was purified by flash chromatography (eluting with ether-hexane 1:9) to afford the *title ester* (1.0 g, 52 %) as a colourless oil;  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3018, 2977, 2873, 1735, 1464, 1329, 1268, 1151, 1034, 740;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.79 (2 H, app. dt,  $J$  10.3, 3.3,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 5.49 (2 H, app. dt,  $J$  10.3, 1.9,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 4.20 (2 H, q,  $J$  7.1,  $\text{O}-\text{CH}_2-\text{CH}_3$ ), 3.94 (2 H, s,  $\text{C}_q-\text{CH}_2-\text{O}$ ), 3.37 (2 H, s,  $\text{O}=\text{C}-\text{CH}_2-\text{C}=\text{O}$ ), 2.65 - 2.61 (2 H, m, ring  $\text{CH}_2$ ), 1.29 (3 H, t,  $J$  7.1,  $\text{CH}_3-\text{CH}_2$ ), 1.07 (3 H, s,  $\text{CH}_3-\text{C}_q$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 166.6 ( $\text{C}=\text{O}$ ), 166.5 ( $\text{C}=\text{O}$ ), 130.3 ( $2 \times$  alkene CH), 125.0 ( $2 \times$  alkene CH), 72.4 ( $\text{C}_q-\text{CH}_2-\text{O}$ ), 61.5 ( $\text{O}-\text{CH}_2-\text{CH}_3$ ), 41.7 ( $\text{O}=\text{C}-\text{CH}_2-\text{C}=\text{O}$ ), 36.7 ( $\text{C}_q$  ring), 26.3 (ring  $\text{CH}_2$ ), 25.2 ( $\text{CH}_3-\text{CH}_2$ ), 14.1 ( $\text{CH}_3-\text{C}_q$ ).

**Malonic acid ethyl ester 1-methyl-4-oxo-cyclohexa-2,5-dienylmethyl ester (112)**



Celite (4.2 g) was added to a cooled (0 °C) suspension of the ester **111** (835 mg, 3.5 mmol), in benzene (20 ml) in a flame dried flask. 5 - 6 M *t*-BuOOH in decane (2.8 ml, 14 mmol, 4 equiv.) was added to the mixture. This was followed by portion-wise addition of pyridinium dichromate (5.3 g, 14 mmol, 4 equiv.) over 10 min. The resulting mixture was stirred at room temperature for 18 hours. After dilution with ether and filtration through a pad of basic alumina type H, the combined solutions were concentrated *in vacuo* affording a brown residue. Purification by column chromatography (eluting with hexane-ether 4:6) afforded the *title dienone 112* (317 mg, 36%) as a pale yellow oil (Found:  $MH^+$  253.1069.  $C_{13}H_{17}O_5$  requires  $M$ , 253.1071);  $\nu_{max}$  (neat)/ $cm^{-1}$  2979, 1733, 1667, 1261, 1149, 1032, 862;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 6.75 (2 H, d,  $J$  10.2,  $2 \times CH=CH-C=O$ ), 6.26 (2 H, d,  $J$  10.2,  $2 \times CH=CH-C=O$ ), 4.14 (2 H, s,  $C_q-CH_2-O$ ), 4.11 (2 H, q,  $J$  7.2,  $O-CH_2-CH_3$ ), 3.29 (2 H, s,  $O=C-CH_2-C=O$ ), 1.23 (3 H, s,  $CH_3-C_q$ ), 1.21 (3 H, t,  $J$  7.2,  $CH_3-CH_2$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 185.6 (ring  $C=O$ ), 166.2 ( $O-C=O$ ), 166.1 ( $O-C=O$ ), 151.5 ( $2 \times CH=CH-C=O$ ), 130.0 ( $2 \times CH=CH-C=O$ ), 69.1 ( $C_q-CH_2-O$ ), 61.8 ( $O-CH_2-CH_3$ ), 41.8 ( $C_q$  ring), 41.3 ( $O=C-CH_2-C=O$ ), 21.8 ( $CH_3-CH_2$ ), 14.1 ( $CH_3-C_q$ );  $m/z$  (APCI) 253 ( $MH^+$ , 37%), 223 (45), 177 (8), 122 (15), 121 (100).

### Cycliation of achiral dienone **112**



#### (a) Cyclisation of dienone **112** using 0.5 M sodium ethoxide.

Freshly prepared 0.5 M sodium ethoxide solution (1.6 ml, 0.8 mmol, 2 equiv.) was added to a solution of dienone **112** (100 mg, 0.397 mmol) in absolute ethanol (10 ml). The resulting mixture was stirred at room temperature for 5 hours under a nitrogen atmosphere, and then quenched with  $NH_4Cl$  saturated solution (20 ml). The organic product was extracted into  $CH_2Cl_2$  ( $2 \times 20$  ml), and the combined extracts

were dried over Na<sub>2</sub>SO<sub>4</sub>. After concentration *in vacuo*, a brown residue was obtained which was purified by flash column chromatography (eluting with ethyl acetate-ether 0.5:9.5), to afford compound **113** as a pale yellow oil (35 mg, 35 %) and *p*-cresol **114** as a brown oil (15 mg, 14 %).

**(b) Cyclisation of dienone 112 using potassium *t*-butoxide**

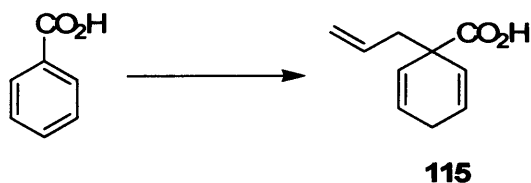
Potassium *t*-butoxide (0.794 mmol, 89.1 mg, 2 equiv.) was added to a solution of dienone **112** (100 mg, 0.397 mmol) in dry THF (10 ml). The resulting mixture was stirred at room temperature for 24 hours under a nitrogen atmosphere, and then, quenched with NH<sub>4</sub>Cl saturated solution. The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml), and the combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* afforded compound **113** as the sole product (92 mg, 92 % yield) as an essentially-pure yellow oil.

**(4*SR*,4*aRS*,8*aRS*)-8*a*-Methyl-3,6-dioxo-3,4,4*a*,5,6,8*a*-hexahydro-1*H*-**

**isochromene-4-carboxylic acid ethyl ester (113):** Found MH<sup>+</sup>, 253.1074. C<sub>13</sub>H<sub>17</sub>O<sub>5</sub> requires M, 253.1071; ν<sub>max</sub> (neat)/cm<sup>-1</sup> 2966, 2924, 1735, 1667, 1258, 1027, 861, 801; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 6.63 (1 H, dd, *J* 10.2, 1.6, H<sup>a</sup>), 6.05 (1 H, d, *J* 10.2, H<sup>b</sup>), 4.23 - 4.15 (4 H, m, 2 × H<sup>g</sup>, H<sup>h</sup>, H<sup>i</sup>, H<sup>j</sup>), 3.32 (1 H, d, *J* 7.3, H<sup>f</sup>), 2.80 – 2.73 (2 H, m, H<sup>d</sup> and H<sup>e</sup>), 2.37 (1 H, dd, *J* 18.8, 4.9, H<sup>c</sup>), 1.26 (3 H, s, Me<sup>a</sup>), 1.24 (3 H, t, *J* 7.2, Me<sup>b</sup>); δ<sub>C</sub> (100 MHz; CDCl<sub>3</sub>) 195.1 (C=O), 168.6 (O-C=O), 168.3 (O-C=O), 151.5 (CH=CH-C=O), 131.1 (CH=CH-C=O), 75.1 (O-CH<sub>2</sub>), 62.7 (O-CH<sub>2</sub>), 51.6 (O=C-CH-C=O), 41.1 (ring junction CH), 39.2 (CH<sub>2</sub>-C=O), 36.2 (C<sub>q</sub> ring), 21.9 (CH<sub>3</sub>-CH<sub>2</sub>), 14.1 (CH<sub>3</sub>-C<sub>q</sub>); *m/z* (APCI) 253 (MH<sup>+</sup>, 18 %), 238 (7), 147 (39), 135 (15), 12 (16), 121 (100).

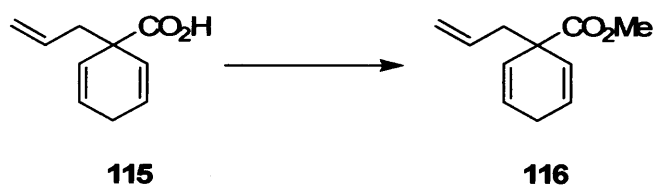
***p*-Cresol (114):** δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 6.97 (2 H, d, *J* 8.3, 2 × CH<sub>3</sub>-C=CH), 6.66 (2 H, d, *J* 8.3, 2 × HO-C=CH). Data are identical with those from an authentic sample.

### 1-Allyl-cyclohexa-2,5-dienecarboxylic acid (115)<sup>11</sup>



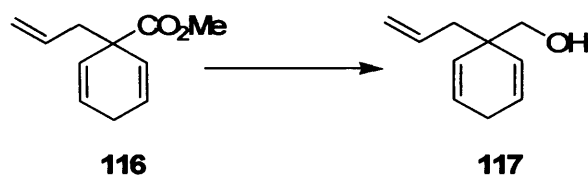
Ammonia (500 cm<sup>3</sup>) was added to benzoic acid (10 g, 82 mmol) in a 1 l round bottomed flask through a dry ice-acetone condenser. With careful stirring, Li (1.6 g, 230 mmol) was added portion-wise until a permanent blue colour persisted. After 15 min at this temperature, allyl bromide (20.2 ml, 234 mmol) was added slowly over a period of 5 min. The ammonia was allowed to evaporate overnight and the residue was dissolved in iced water. Dilute H<sub>2</sub>SO<sub>4</sub> was added until pH 1 - 2 was reached. The solution was then extracted into diethyl ether (3 × 200 ml). The combined ethereal extracts were dried over MgSO<sub>4</sub>. The solvent was removed *in vacuo* to give a yellow oil. This oil was washed with petroleum ether, and filtered to separate a dark residue. The filtrate was concentrated under reduced pressure to afford *the title acid* (12.6 g, 91 %) as an essentially-pure colourless oil which solidified upon standing, m.p. 50 - 52 °C (Found M<sup>+</sup>, 164.0831. C<sub>10</sub>H<sub>12</sub>O<sub>2</sub> requires M, 164.0832);  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3034, 1699, 1639, 1416, 1269, 918;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 11.42 (1 H, broad s, OH), 5.85 (2 H, app. dt, *J* 10.4, 3.3, 2 × CH=CH-CH<sub>2</sub>), 5.69 (2 H, app. dt, *J* 10.4, 2.0, 2 × CH=CH-CH<sub>2</sub>), 5.66 - 5.56 (1 H, m, CH<sub>2</sub>=CH), 5.08-4.96 (2 H, m, CH<sub>2</sub>=CH), 2.66 - 2.50 (2 H, m, ring CH<sub>2</sub>), 2.39 (2 H, d, *J* 7.2, CH<sub>2</sub>-C<sub>q</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 180.8 (C=O), 132.9 (CH=CH<sub>2</sub>), 126.4 (2 × alkene CH), 126.2 (2 × alkene CH), 118.4 (CH<sub>2</sub>=CH), 47.6 (C<sub>q</sub> ring), 44.1 (CH<sub>2</sub>-C<sub>q</sub>), 26.1 (ring CH<sub>2</sub>); *m/z* (EI) 164 (M<sup>+</sup>, 6 %), 123 (20), 105 (28), 91 (20), 79 (100), 77 (82), 51 (17), 41 (26).

### 1-Allyl-cyclohexa-2,5-dienecarboxylic acid methyl ester (116)



1-Allylcyclohexa-2,5-diene-1-carboxylic acid **115** (17.4 g, 106.1 mmol) was dissolved in absolute methanol (175 ml) and conc. H<sub>2</sub>SO<sub>4</sub> (0.36 ml) was added. After refluxing the reaction mixture for 24 h, most of the solvent was evaporated. The remaining solution was neutralised by addition of saturated NaHCO<sub>3</sub> solution. The organic compound was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 100 ml), dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford the *title ester* (16.3 g, 86 %) as an essentially-pure yellow oil;  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3033, 2950, 2908, 1736, 1639, 1435, 1237, 1029, 918, 797, 738;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>), 5.90 (2 H, app. dt, *J* 10.4, 3.3, 2 × CH=CH-CH<sub>2</sub>), 5.77 (2 H, app. dt, *J* 10.4, 2.0, 2 × CH=CH-CH<sub>2</sub>), 5.74 - 5.61 (1 H, m, CH=CH<sub>2</sub>), 5.10 - 5.01 (2 H, m, CH<sub>2</sub>=CH), 3.70 (3 H, s, CH<sub>3</sub>), 2.73 - 2.57 (2 H, m, ring CH<sub>2</sub>), 2.45 (2 H, d, *J* 7.2, CH<sub>2</sub>-C<sub>q</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 174.7 (C=O), 133.2 (CH=CH<sub>2</sub>), 127.0 (2 × alkene CH), 125.7 (2 × alkene CH), 118.0 (CH<sub>2</sub>=CH), 52.1 (CH<sub>3</sub>), 47.7 (C<sub>q</sub> ring), 44.4 (CH<sub>2</sub>-C<sub>q</sub>), 26.1 (ring CH<sub>2</sub>); *m/z* (EI) 178 (M<sup>+</sup>, 5 %), 137 (28), 105 (51), 91 (87), 79 (100), 77 (100), 59 (72).

**(1-Allyl-cyclohexa-2,5-dienyl)-methanol (117)**

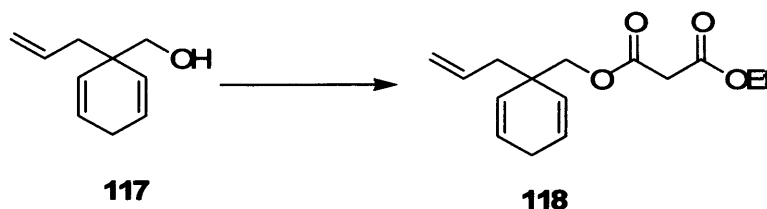


To a stirred suspension of LiAlH<sub>4</sub> (5.1 g, 134.4 mmol) in dry THF (115 ml) under a nitrogen atmosphere at room temperature was added a solution of ester **116** (16.2 g, 91 mmol) in dry THF (25 ml). The mixture was stirred at room temperature for 1 hour, then 15 % aqueous NaOH solution (5.1 ml) was added carefully followed by addition of water (14.8 ml) and stirring was continued at room temperature for 48 h. Filtration and concentration under reduced pressure afforded the *title alcohol* **117** (11.4 g, 83 %) as an essentially-pure pale yellow oil;  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3388, 3017, 2916, 1707, 1638, 1438, 1239, 1060, 1021, 914, 745, 710;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 5.83 (2 H, app. dt, *J* 10.3, 3.3, 2 × CH=CH-CH<sub>2</sub>), 5.65 - 5.56 (1 H, m, CH=CH<sub>2</sub>), 5.31 (2 H, app. dt, *J* 10.3, 2.0, 2 × CH=CH-CH<sub>2</sub>), 4.91 - 4.84 (2 H, m, CH<sub>2</sub>=CH), 3.25 (2 H, s, CH<sub>2</sub>-O), 2.53 - 2.49 (2 H, m, ring CH<sub>2</sub>), 1.96 (2 H, d, *J* 7.2, CH<sub>2</sub>-C<sub>q</sub>);  $\delta_{\text{C}}$



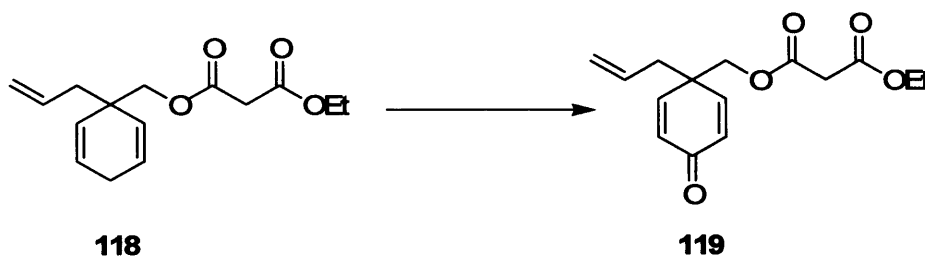
(100 MHz; CDCl<sub>3</sub>) 134.3 (CH=CH<sub>2</sub>), 129.5 (2 × alkene CH), 127.4 (2 × alkene CH), 117.1 (CH<sub>2</sub>=CH), 69.9 (O-CH<sub>2</sub>), 42.9 (C<sub>q</sub> ring), 42.1 (CH<sub>2</sub>-C<sub>q</sub>), 26.1 (ring CH<sub>2</sub>).

**Malonic acid 1-allylcyclohexa-2,5-dienylmethyl ester ethyl ester (118)**



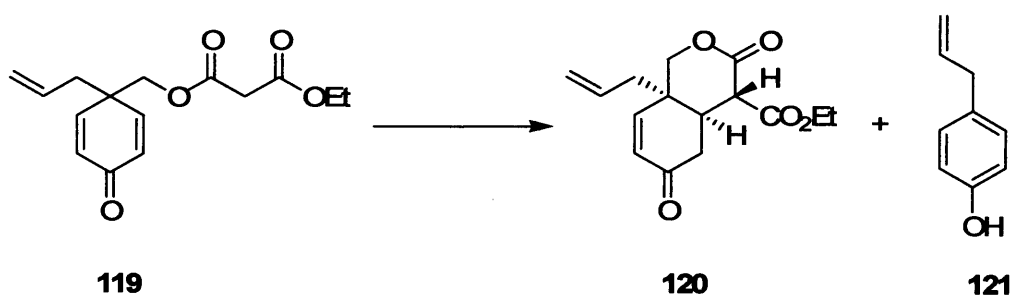
Ethyl malonyl chloride (1.02 g, 0.86 ml, 6.8 mmol, 1.1 equiv.) dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was added to a solution of (1-allyl-cyclohexa-2,5-dienyl)-methanol **117** (924 mg, 6.2 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 ml). Triethylamine (0.69 g, 0.95 ml, 6.8 mmol, 1.1 equiv.) and DMAP (few crystals) were added. After stirring the resulting mixture at room temperature for 24 hours, aqueous 2 M HCl solution (15 ml) was added and the organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 ml). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford the *title ester* **118** as an essentially-pure yellow oil (1.5 g, 94 %) which was used without further purification;  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 2981, 2818, 1735, 1639, 1456, 1415, 1370, 1004, 916, 735;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 5.88 (2 H, app. dt, *J* 10.4, 3.3, 2 × CH=CH-CH<sub>2</sub>), 5.70 (1 H, ddt, *J* 18.2, 10.6, 7.2, CH=CH<sub>2</sub>), 5.48 (2 H, app. dt, *J* 10.4, 2.0, 2 × CH=CH-CH<sub>2</sub>), 5.07 - 5.01 (2 H, m, CH<sub>2</sub>=CH), 4.22 (2 H, q, *J* 7.1, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.00 (2 H, s, C<sub>q</sub>-CH<sub>2</sub>-O), 3.39 (2 H, s, O=C-CH<sub>2</sub>-C=O), 2.65 - 2.61 (2 H, m, ring CH<sub>2</sub>), 2.18 (2 H, d, *J* 7.2, CH<sub>2</sub>=CH-CH<sub>2</sub>), 1.31 (3 H, t, *J* 7.1, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 166.5 (C=O), 166.4 (C=O), 133.9 (CH=CH<sub>2</sub>), 128.7 (2 × alkene CH), 126.3 (2 × alkene CH), 117.5 (CH<sub>2</sub>=CH), 71.2 (C<sub>q</sub>-CH<sub>2</sub>-O), 61.5 (O-CH<sub>2</sub>-CH<sub>3</sub>), 42.1 (O=C-CH<sub>2</sub>-C=O), 41.6 (=CH-CH<sub>2</sub>-C<sub>q</sub>), 40.2 (C<sub>q</sub> ring), 26.5 (ring CH<sub>2</sub>), 14.1 (CH<sub>3</sub>).

**Malonic acid 1-allyl-4-oxo-cyclohexa-2,5-dienylmethyl ester ethyl ester (119)**



Celite (6.1 g) was added to a cooled (0 °C) suspension of the ester **118** (1.35 g, 5.1 mmol) in benzene (25 ml) in a flame dried flask. 5 - 6 M *t*-BuOOH in decane (4.1 ml, 20.5 mmol, 4 equiv.) was added. This was followed by portion-wise addition of pyridinium dichromate (7.7 g, 20.5 mmol, 4 equiv.) over 10 min. The resulting mixture was stirred at room temperature for 18 hours. After dilution with ether and filtration through a pad of basic alumina type H, the combined solutions were concentrated *in vacuo* to afford a brown oil. The resulting oil was purified by column chromatography (eluting with CH<sub>2</sub>Cl<sub>2</sub>-methanol 9:1) to afford the *title enone* (725 mg, 51 %) as a yellow oil; (Found MH<sup>+</sup> 279.1225. C<sub>15</sub>H<sub>19</sub>O<sub>5</sub> requires M, 279.1227);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 2982, 1734, 1667, 1628, 1445, 1405, 1370, 1331, 1262, 1149, 1033, 926, 862;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 6.74 (2 H, d, *J* 10.3, 2 × CH=CH-C=O), 6.31 (2 H, d, *J* 10.3, 2 × CH=CH-C=O), 5.50 (1H, ddt *J* 17.2, 10.4, 7.2, CH=CH<sub>2</sub>), 5.07 - 5.00 (2 H, m, CH<sub>2</sub>=CH), 4.17 (2 H, s, C<sub>q</sub>-CH<sub>2</sub>-O), 4.11 (2 H, q, *J* 7.1, O-CH<sub>2</sub>-CH<sub>3</sub>), 3.29 (2 H, s, O=C-CH<sub>2</sub>-C=O), 2.35 (2 H, d, *J* 7.2, =CH-CH<sub>2</sub>-C<sub>q</sub>), 1.20 (3 H, t, *J* 7.1, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 185.8 (C=O), 166.1 (O-C=O), 166.0 (O-C=O), 150.0 (2 × CH=CH-C=O), 131.2 (2 × CH=CH-C=O), 129.6 (CH<sub>2</sub>=CH), 120.0 (CH=CH<sub>2</sub>), 68.1 (C<sub>q</sub>-CH<sub>2</sub>-O), 61.8 (O-CH<sub>2</sub>-CH<sub>3</sub>), 45.5 (C<sub>q</sub> ring), 41.3 (O=C-CH<sub>2</sub>-C=O), 39.7 (=CH-CH<sub>2</sub>-C<sub>q</sub>), 14.1 (CH<sub>3</sub>); *m/z* (APCI) 279 (MH<sup>+</sup>, 34 %), 148 (13), 147 (100).

**Cyclisation of achiral allyl enone 119**



**(a) Cyclisation of dienone 119 using 0.5 M sodium ethoxide.**

Freshly prepared 0.5 M sodium ethoxide solution (4.2 ml, 2.1 mmol, 1.7 equiv.) was added to a solution of dienone **119** (342 mg, 1.23 mmol) in absolute ethanol (20 ml). The mixture was stirred at room temperature for 20 hours under a nitrogen atmosphere, and then quenched with saturated NH<sub>4</sub>Cl solution (20 ml). The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 ml). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a dark brown oil. Purification by flash column chromatography (eluted in gradient mode from CH<sub>2</sub>Cl<sub>2</sub>-hexane 2:1 to neat ethyl acetate) afforded compound **121** as a colourless oil (45 mg, 27 %) and compound **120** (which eluted from EtOAc fractions) as a pale yellow oil (105 mg, 31 %) respectively.

**(b) Cyclisation of dienone 119 using potassium *t*-butoxide**

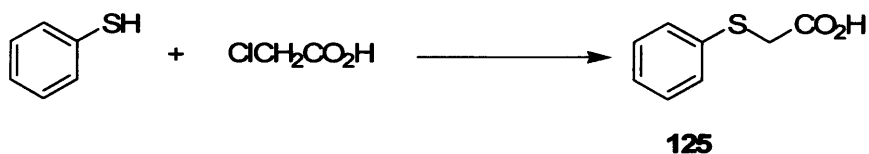
Potassium *t*-butoxide (161.5 mg, 1.44 mmol, 2 equiv.) was added to a solution of dienone **119** (200 mg, 0.72 mmol) in dry THF (20 ml). The mixture was stirred at room temperature for 28 hours under a nitrogen atmosphere, and then quenched with saturated NH<sub>4</sub>Cl solution. The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to afford a dark brown oil. Purification by column chromatography (eluted in gradient mode from CH<sub>2</sub>Cl<sub>2</sub>-hexane 2:1 to neat ethyl acetate) afforded phenol **121** as a colourless oil (8 mg, 8 %) and **120** which eluted from EtOAc fractions as a pale yellow oil (75 mg, 38 %) respectively.

**4-Allyl phenol (121):** yellow (8 mg, 8.3 %);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3366, 3077, 2976, 1612, 1513, 1443, 1234, 994, 914, 825;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 6.98 (2 H, d, *J* 8.4, 2 × aromatic CH), 6.69 (2 H, d, *J* 8.4, 2 × aromatic CH), 5.87 (1 H, ddt, *J* 17.0, 10.5, 6.6, CH<sub>2</sub>=CH-CH<sub>2</sub>), 5.01 - 4.93 (2 H, m, CH<sub>2</sub>=CH), 3.24 (2 H, d, *J* 6.6, C<sub>q</sub>-CH<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 153.8 (C<sub>q</sub>-OH), 137.9 (CH=CH<sub>2</sub>), 132.3 (C<sub>q</sub>-CH<sub>2</sub>), 129.7 (2 × aromatic CH), 115.5 (CH=CH<sub>2</sub>), 115.2 (2 × aromatic CH), 39.3 (C<sub>q</sub>-CH<sub>2</sub>).

**(4*SR*,4*aRS*,8*aRS*)-8*a*-Allyl-3,6-dioxo-3,4,4*a*,5,6,8*a*-hexahydro-1*H*-isochromene-4-carboxylic acid ethyl ester (120):** Pale yellow oil (75 mg, 37.5 %) (Found: MH<sup>+</sup>

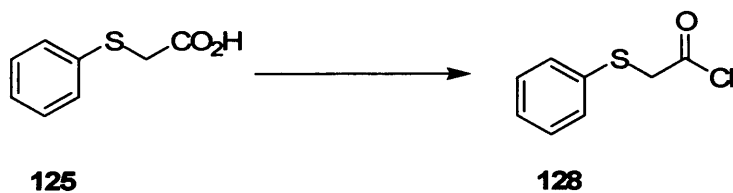
279.1224.  $C_{15}H_{19}O_5$  requires M, 279.1227);  $\nu_{\max}$  (neat)/ $cm^{-1}$  2979, 1732, 1682, 1398, 1253, 1155, 929, 790;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 6.59 (1 H, dd,  $J$  10.3, 1.5,  $\underline{CH=CH-C=O}$ ), 6.11 (1 H, d,  $J$  10.3,  $\underline{CH=CH-C=O}$ ), 5.70 (1 H, app. ddt,  $J$  17.1, 10.0, 7.5,  $\underline{CH=CH_2}$ ), 5.24 - 5.14 (2 H, m,  $\underline{CH_2=CH}$ ), 4.25 - 4.15 (4 H, m,  $2 \times O-\underline{CH_2}$ ), 3.32 (1 H, d,  $J$  7.6,  $O=C-CH-C=O$ ), 2.86 (1 H, dddd,  $J$  7.6, 5.4, 3.8, 1.5, ring junction CH), 2.76 (1 H, dd,  $J$  17.4, 5.4 one of  $O=C-CH_2$ ), 2.45 (1 H, dd,  $J$  14.1, 7.5, one of  $\underline{CH_2=CH-CH_2}$ ), 2.35 (1 H, dd,  $J$  17.4, 3.8, one of  $O=C-CH_2$ ), 2.31 (1 H, dd,  $J$  14.1, 7.5, one of one of  $\underline{CH_2=CH-CH_2}$ ), 1.24 (3 H, t,  $J$  7.1,  $CH_3$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 195.1 ( $C=O$ ), 168.3 ( $O-C=O$ ), 166.7 ( $O-C=O$ ), 150.2 ( $\underline{CH=CH-C=O}$ ), 131.6 ( $\underline{CH=CH-C=O}$ ), 130.6 ( $\underline{CH_2=CH}$ ), 121.3 ( $\underline{CH_2=CH}$ ), 73.1 ( $O-\underline{CH_2-C_q}$ ), 62.7 ( $O-\underline{CH_2-CH_3}$ ), 51.7 ( $O=C-\underline{CH-C=O}$ ), 40.8 ( $\underline{CH_2-C=O}$ ), 39.3 ( $\underline{CH_2=CH-CH_2}$ ), 39.2 ( $C_q$  ring), 38.6 (ring junction CH), 14.1 ( $CH_3$ );  $m/z$  (APCI) 279 ( $MH^+$ , 27 %), 116 (6), 115 (100), 86 (16).

## 2-Phenysulfanylacetic acid (**125**)<sup>36</sup>



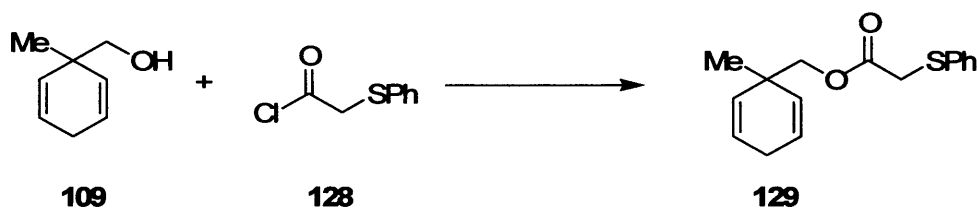
Chloroacetic acid (10.1 mg, 107 mmol) was added to a solution of benzenethiol (10.69 g, 10 ml, 97 mmol) in aqueous sodium hydroxide (8.2 g, 205 mmol in 200 ml  $H_2O$ ). The mixture was refluxed for 3.5 hours, then cooled and acidified with aqueous 2 M HCl solution to pH 1 - 2. The resulting white precipitate was isolated by filtration and recrystallised from water to afford *the title acid* **125** (11 g, 67 %) as a white powder, m.p. 61 - 63 °C (lit. m.p. 63.5 °C);  $\nu_{\max}$  (KBr)/ $cm^{-1}$  3448, 2922, 2853, 1704, 1462, 1197, 736;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 7.47 - 7.41 (2 H, m,  $2 \times$  aromatic CH), 7.37 - 7.30 (2 H, m,  $2 \times$  aromatic CH), 7.29 - 7.25 (1 H, m,  $p$ -aromatic CH), 3.69 (2 H, s,  $CH_2-S$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 175.6 ( $C=O$ ), 134.5 ( $C_q-S$ ), 130.0 ( $2 \times o$ -aromatic CH), 129.2 ( $2 \times m$ -aromatic CH), 127.3 ( $p$ -aromatic CH), 36.6 ( $CH_2-S$ ).

## 2-Phenysulfanylacetyl chloride (**128**)<sup>38</sup>



Thionyl chloride (27 ml) was added to 2-phenylsulfanylacetic acid **125** (13.7 g, 81.5 mmol), and the resulting mixture was refluxed at 70 °C for 2 hours. The excess thionyl chloride was removed *in vacuo* at 60 °C to afford the *title acid chloride* **128** (15 g, 99 %) as an essentially-pure brown oil which was used without further purification;  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3034, 2980, 2931, 2873, 1785, 1452, 1417, 904, 787, 710;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.36 - 7.32 (2 H, m, 2  $\times$  aromatic CH), 7.27 - 7.17 (3 H, m, 3  $\times$  aromatic CH), 3.94 (2 H, s,  $\text{CH}_2$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 169.9 (C=O), 132.9 ( $\text{C}_q\text{-S}$ ), 131.6 (2  $\times$  *o*-aromatic CH), 129.5 (2  $\times$  *m*-aromatic CH), 128.3 (*p*-aromatic CH), 48.6 ( $\text{CH}_2\text{-S}$ ).

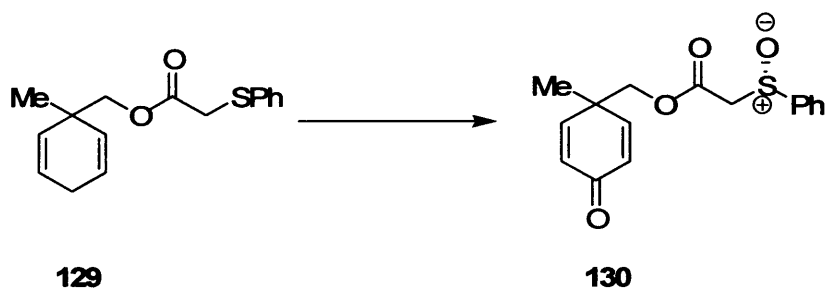
## Phenylsulfanylacetic acid 1-methylcyclohexa-2,5-dienyl methyl ester (**129**)



2-Phenylsulfanylacetyl chloride **128** (9.2 g, 49.5 mmol, 1.02 equiv.) dissolved in dry  $\text{CH}_2\text{Cl}_2$  (40 ml) was added to a solution of the alcohol **109** (6 g, 48.39 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (400 ml). Triethylamine (10 ml, 71.7 mmol, 1.5 equiv.) and DMAP (few crystals) were added. The resulting mixture was stirred at room temperature for 72 hours, and then quenched with aqueous 2 M HCl solution (30 ml). The organic material was extracted into  $\text{CH}_2\text{Cl}_2$  (3  $\times$  50 ml) and dried over  $\text{MgSO}_4$ . After the solvent was removed under reduced pressure, the remaining brown solution was purified by flash chromatography (eluting with ether-hexane 0.5:9.5) to afford the

*title compound 129* (10.2 g, 77 %) as a pale yellow oil;  $\nu_{\max}$  (neat)/ $\text{cm}^{-1}$  3017, 2962, 2869, 1736, 1538, 1482, 1270, 1136, 1000, 740;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.42 – 7.21 (5 H, m, aromatic CH), 5.76 (2 H, app. dt,  $J$  10.3, 3.3,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 5.45 (2 H, app. dt,  $J$  10.3, 2.0,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 3.92 (2 H, s, O- $\text{CH}_2$ ), 3.67 (2 H, s, S- $\text{CH}_2$ ), 2.63 – 2.59 (2 H, m, ring  $\text{CH}_2$ ), 1.03 (3 H, s,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 169.8 (C=O), 135.3 ( $\text{C}_q\text{-S}$ ), 130.3 ( $2 \times o\text{-aromatic CH}$ ), 129.5 ( $2 \times \text{alkene or } m\text{-aromatic CH}$ ), 129.0 ( $2 \times \text{alkene or } m\text{-aromatic CH}$ ), 126.8 ( $p\text{-aromatic CH}$ ), 125.0 ( $2 \times \text{alkene CH}$ ), 72.5 (O- $\text{CH}_2$ ), 36.7 ( $\text{C}_q\text{ ring}$ ), 36.5 (S- $\text{CH}_2$ ), 26.3 (ring  $\text{CH}_2$ ), 25.2 ( $\text{CH}_3$ );  $m/z$  (APCI) 275 ( $\text{MH}^+$ , 3%), 185 (34), 167 (37), 125 (72), 121 (100).

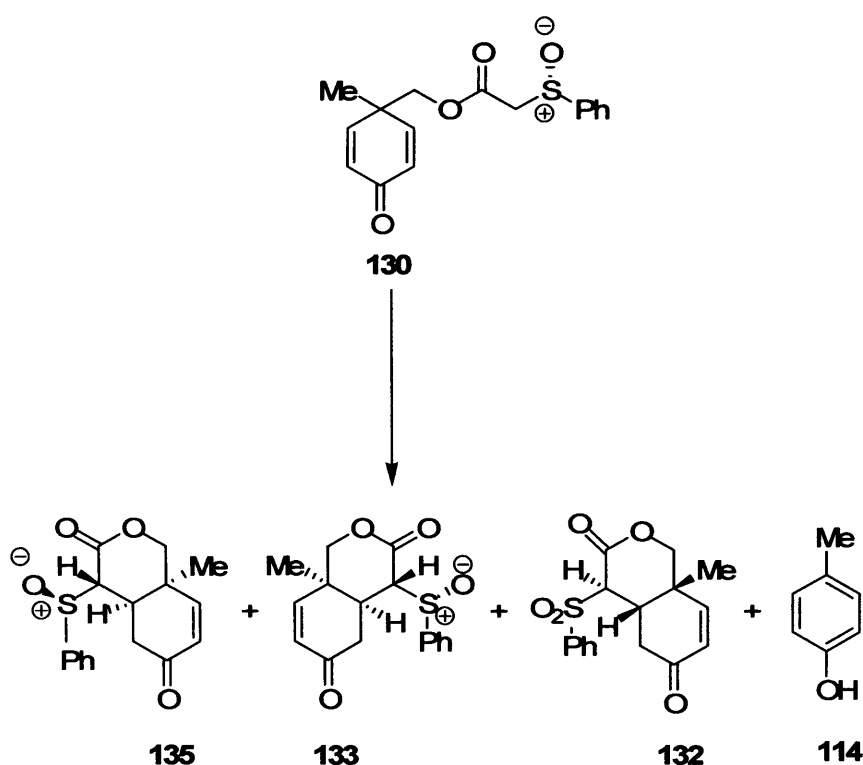
**Benzenesulfinylacetic acid 1-methyl-4-oxocyclohexa-2,5-dienyl methyl ester (130)**



Celite (24 g) was added to a suspension of ester **129** (4.1 g, 15 mmol) in dry benzene (190 ml) at 0 °C in a flame dried flask. 5 - 6 M *t*-BuOOH in decane (12.7 ml, 63.5 mmol, 4.2 equiv.) was added followed by portion-wise addition of pyridinium dichromate (23.6 g, 63.5 mmol, 4.2 equiv.) over 1 hour. After the addition was complete, the reaction mixture was stirred at that temperature for a further 2 hours, then the cooling bath was removed and stirring was continued at room temperature for 18 hours. The resulting mixture was diluted with ethyl acetate, filtered and concentrated *in vacuo*. The remaining brown viscous oil was purified by column chromatography (eluting with ether–ethyl acetate 3:1) to give the *title dienone 130* (2.1 g, 45 %) as a pale yellow waxy solid, m.p. 74 - 75 °C (Found:  $\text{MH}^+$  305.0842.  $\text{C}_{16}\text{H}_{17}\text{SO}_4$  requires M, 305.0842);  $\nu_{\max}$  ( $\text{CH}_2\text{Cl}_2$ )/ $\text{cm}^{-1}$  2924, 1738, 1666, 1627, 1444, 1258, 1049, 862, 650;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.61 - 7.57 (2 H, m,  $2 \times \text{aromatic CH}$ ), 7.51 - 7.47 (3 H, m,  $3 \times \text{aromatic CH}$ ), 6.71 - 6.66 (2 H, m,  $2 \times \text{CH}=\text{CH}-\text{C}=\text{O}$ ), 6.25 - 6.20 (2 H, m,  $2 \times \text{CH}=\text{CH}-\text{C}=\text{O}$ ), 4.19 (1 H, d,  $J$  10.7, one of O- $\text{CH}_2$ ), 4.09 (1 H, d,  $J$

10.7, one of O-CH<sub>2</sub>), 3.70 (1 H, d, *J* 13.7, one of S-CH<sub>2</sub>), 3.58 (1 H, d, *J* 13.7, one of S-CH<sub>2</sub>), 1.20 (3 H, s, CH<sub>3</sub>);  $\delta_C$  (100 MHz; CDCl<sub>3</sub>) 185.6 (ring C=O), 164.4 (O-C=O), 151.3 ( $\underline{\text{CH}}=\text{CH}-\text{C}=\text{O}$ ), 151.2 ( $\underline{\text{CH}}=\text{CH}-\text{C}=\text{O}$ ), 142.8 (C<sub>q</sub>-S), 131.9 (*p*-aromatic CH), 130.1 ( $\text{CH}=\underline{\text{CH}}-\text{C}=\text{O}$ ), 130.1 ( $\text{CH}=\underline{\text{CH}}-\text{C}=\text{O}$ ), 129.6 (2  $\times$  *o*-aromatic CH), 124.1 (2  $\times$  *m*-aromatic CH), 69.7 (O-CH<sub>2</sub>), 61.3 (CH<sub>2</sub>-SO), 41.6 (C<sub>q</sub> ring), 21.8 (CH<sub>3</sub>); *m/z* (APCI) 305 (MH<sup>+</sup>, 100 %), 275 (13), 197 (8), 185 (7), 167 (3), 121 (100).

### Cyclisation of dienone (130)

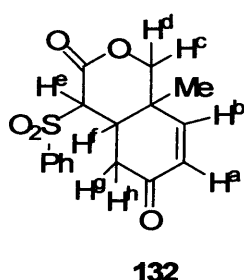


In a flame-dried flask and under a nitrogen atmosphere, potassium *t*-butoxide (7 mmol, 0.78 g, 2 equiv.) was added to a cooled solution of dienone **130** (1.059 g, 3.48 mmol) in dry THF (130 ml) at 0 °C. The mixture was stirred at this temperature for 5.5 hours, and then at room temperature for 17.5 hours. The resulting mixture was quenched with saturated NH<sub>4</sub>Cl solution (50 ml), and the organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  50 ml). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to afford 592 mg of a crude mixture of compounds **114**, **132**, **133**, and **135** as a golden solid. Purification by flash chromatography (eluting with CH<sub>2</sub>Cl<sub>2</sub>-ethyl acetate 9.3:0.7) afforded the pure products in order as follows:

***p*-Cresol (114):** Yellow oil (12.1 mg, 2.2 %). Data as previously reported (page 158).

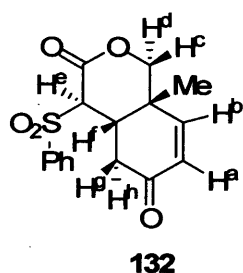
**(4*RS*,4*aSR*,8*aRS*)-4-Benzenesulfonyl-8*a*-methyl-1,4*a*,5,8*a*-tetrahydro-4*H*-isochromene-3,6-dione (132):** Off-white solid (21.1 mg, 1.9 %), m.p. 185 - 186 °C (Found:  $\text{MNH}_4^+$  338.1062.  $\text{C}_{16}\text{H}_{20}\text{O}_5\text{NS}$  requires  $\text{M}$ , 338.1057);  $\nu_{\text{max}}$  ( $\text{CH}_2\text{Cl}_2$ )/ $\text{cm}^{-1}$  3056, 2940, 1737, 1680, 1319, 1265, 1149, 736;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.80 (2 H, app. dd,  $J$  8.4, 1.2,  $2 \times o$ -aromatic CH), 7.66 (1 H, app. tt,  $J$  7.4, 1.2,  $p$ -aromatic CH), 7.56 - 7.50 (2 H, m,  $2 \times m$ -aromatic CH), 6.63 (1 H, dd,  $J$  10.3, 2.0,  $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 6.03 (1 H, d,  $J$  10.3,  $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 4.51 (1 H, d,  $J$  11.3, one of O- $\text{CH}_2$ ), 4.17 (1 H, d,  $J$  11.3, one of O- $\text{CH}_2$ ), 3.72 (1 H, d,  $J$  5.4, CH- $\text{SO}_2$ ), 3.3 (1 H, app. tt,  $J$  5.0, 2.5, ring junction CH), 2.95 (1 H, dd,  $J$  17.5, 5.0, one of  $\text{CH}_2-\text{C}=\text{O}$ ), 2.56 (1 H, dd,  $J$  17.5, 2.5, one of  $\text{CH}_2-\text{C}=\text{O}$ ), 1.34 (3 H, s,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 194.8 (C=O), 162.4 (O-C=O), 152.0 ( $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 136.0 ( $\text{C}_q-\text{S}$ ), 135.0 ( $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 132.0 ( $p$ -aromatic CH), 129.4 ( $2 \times o$ -aromatic CH), 129.3 ( $2 \times m$ -aromatic CH), 75.2 (O- $\text{CH}_2$ ), 69.6 (CH- $\text{SO}_2$ ), 40.5 ( $\text{CH}_2-\text{C}=\text{O}$ ), 38.4 (ring junction CH), 36.9 ( $\text{C}_q$  ring), 20.3 ( $\text{CH}_3$ );  $m/z$  (APCI) 321 ( $\text{MH}^+$ , 100 %), 319 (11), 121 (16).

$^1\text{H} - ^1\text{H}$  COSY experiment showed the following correlations



$\text{H}^b$ ,  $\delta = 6.63$ , showed a cross peak to  $\text{H}^a$  &  $\text{H}^f$   
 $\text{H}^a$ ,  $\delta = 6.03$ , showed a cross peak to  $\text{H}^b$   
 $\text{H}^c$ ,  $\delta = 4.51$ , showed a cross peak to  $\text{H}^d$   
 $\text{H}^d$ ,  $\delta = 4.17$ , showed a cross peak to  $\text{H}^e$   
 $\text{H}^e$ ,  $\delta = 3.72$ , showed a cross peak to  $\text{H}^f$   
 $\text{H}^f$ ,  $\delta = 3.33$ , showed a cross peak to  $\text{H}^g$ ,  $\text{H}^b$ ,  $\text{H}^i$  &  $\text{H}^j$   
 $\text{H}^g$ ,  $\delta = 2.95$ , showed a cross peak to  $\text{H}^h$  &  $\text{H}^i$   
 $\text{H}^h$ ,  $\delta = 2.56$ , showed a cross peak to  $\text{H}^g$  &  $\text{H}^i$

NOESY experiment showed the following correlations

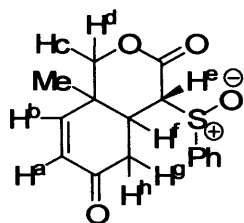


$\text{H}^b$ ,  $\delta = 6.63$ , showed a cross peak to  $\text{H}^a$ ,  $\text{H}^f$  &  $\text{CH}_3$   
 $\text{H}^a$ ,  $\delta = 6.03$ , showed a cross peak to  $\text{H}^b$   
 $\text{H}^c$ ,  $\delta = 4.51$ , showed a cross peak to  $\text{H}^d$ ,  $\text{H}^f$  &  $\text{CH}_3$   
 $\text{H}^d$ ,  $\delta = 4.17$ , showed a cross peak to  $\text{H}^e$ ,  $\text{H}^f$  &  $\text{CH}_3$   
 $\text{H}^e$ ,  $\delta = 3.72$ , showed a cross peak to  $\text{H}^f$ , &  $\text{H}^i$   
 $\text{H}^f$ ,  $\delta = 3.33$ , showed a cross peak to  $\text{H}^g$ ,  $\text{H}^b$ ,  $\text{H}^i$  &  $\text{CH}_3$   
 $\text{H}^g$ ,  $\delta = 2.95$ , showed a cross peak to  $\text{H}^h$ ,  $\text{H}^i$  &  $\text{CH}_3$   
 $\text{H}^h$ ,  $\delta = 2.56$ , showed a cross peak to  $\text{H}^g$  &  $\text{H}^i$   
 $\text{CH}_3$ ,  $\delta = 1.34$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^c$ ,  $\text{H}^d$ ,  $\text{H}^f$  &  $\text{H}^g$



**(*S<sub>SR</sub>*,*4R**S*,*4aSR*,*8aR**S*)-4-Benzenesulfinyl-8a-methyl-1,4a,5,8a-tetrahydro-4H-isochromene-3,6-dione (133):** Yellow solid (44.3 mg, 4.2 %), m.p. 108 - 110 °C (Found:  $\text{MNH}_4^+$  322.1111.  $\text{C}_{16}\text{H}_{20}\text{SO}_4\text{N}$  requires M, 322.1108);  $\nu_{\text{max}}$  ( $\text{CDCl}_3$ )/ $\text{cm}^{-1}$  1737, 1685, 1445, 1404, 1247, 1060, 909, 733;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.61 - 7.56 (2 H, m, 2  $\times$  aromatic CH), 7.55 - 7.50 (3 H, m, 3  $\times$  aromatic CH), 6.63 (1 H, dd,  $J$  10.2, 1.8,  $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 5.98 (1 H, d,  $J$  10.2,  $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 4.32 (1 H, d,  $J$  11.2, one of O- $\text{CH}_2$ ), 4.05 (1 H, d,  $J$  11.2, one of O- $\text{CH}_2$ ), 3.25 (1 H, d,  $J$  5.1, CH-SO), 2.91 - 2.85 (1 H, m, ring junction CH), 2.36 (1 H, dd,  $J$  17.3, 5.2, one of  $\text{CH}_2-\text{C}=\text{O}$ ), 1.23 (3 H, s,  $\text{CH}_3$ ), 0.93 (1 H, dd,  $J$  17.3, 2.7, one of  $\text{CH}_2-\text{C}=\text{O}$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 195.0 ( $\text{C}=\text{O}$ ), 167.0 ( $\text{O}-\text{C}=\text{O}$ ), 152.9 ( $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 140.2 ( $\text{C}_q-\text{S}$ ), 132.3 ( $p$ -aromatic CH), 131.7 ( $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 129.8 (2  $\times$   $o$ -aromatic CH), 124.0 (2  $\times$   $m$ -aromatic CH), 74.7 (O- $\text{CH}_2$ ), 69.4 (CH-SO), 39.8 ( $\text{CH}_2-\text{C}=\text{O}$ ), 36.5 ( $\text{C}_q$  ring), 33.6 (ring junction CH), 20.4 ( $\text{CH}_3$ );  $m/z$  (APCI) 305 ( $\text{MH}^+$ , 39 %), 235 (35), 197 (10), 180 (12), 179 (100), 149 (10), 125 (37).

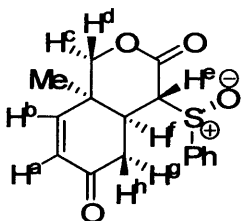
$^1\text{H} - ^1\text{H}$  COSY experiment showed the following correlations



133

$\text{H}^b$ ,  $\delta = 6.63$ , showed a cross peak to  $\text{H}^a$  &  $\text{H}^f$   
 $\text{H}^a$ ,  $\delta = 5.98$ , showed a cross peak to  $\text{H}^b$   
 $\text{H}^f$ ,  $\delta = 4.32$ , showed a cross peak to  $\text{H}^d$   
 $\text{H}^d$ ,  $\delta = 4.05$ , showed a cross peak to  $\text{H}^f$   
 $\text{H}^e$ ,  $\delta = 3.25$ , showed a cross peak to  $\text{H}^f$   
 $\text{H}^f$ ,  $\delta = 2.91-2.85$ , showed a cross peak to  $\text{H}^a$ ,  $\text{H}^b$ ,  $\text{H}^e$  &  $\text{H}^h$   
 $\text{H}^g$ ,  $\delta = 2.36$ , showed a cross peak to  $\text{H}^i$  &  $\text{H}^f$   
 $\text{H}^i$ ,  $\delta = 0.93$ , showed a cross peak to  $\text{H}^g$  &  $\text{H}^f$

nOe experiment showed the following enhancements

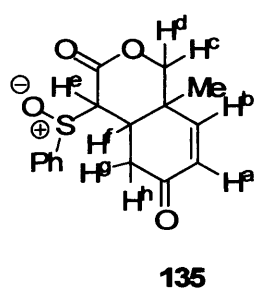


133

Irradiation point at  $\delta = 0.93$  ( $\text{H}^i$ ) gave a positive peak to  $\text{H}^g$  &  $\text{H}^f$   
Irradiation point at  $\delta = 1.23$  ( $\text{CH}_3$ ) gave a positive peak to  $\text{H}^b$ ,  $\text{H}^c$ ,  $\text{H}^d$ ,  $\text{H}^e$  &  $\text{H}^f$   
Irradiation point at  $\delta = 2.36$  ( $\text{H}^g$ ) gave a positive peak to  $\text{H}^i$ ,  $\text{H}^f$  &  $\text{CH}_3$   
Irradiation point at  $\delta = 2.91-2.85$  ( $\text{H}^f$ ) gave a positive peak to  $\text{H}^b$ ,  $\text{H}^e$ ,  $\text{H}^c$  &  $\text{CH}_3$   
Irradiation point at  $\delta = 3.25$  ( $\text{H}^e$ ) gave a positive peak to ,  $\text{H}^f$  &  $\text{H}^i$   
Irradiation point at  $\delta = 6.63$  ( $\text{H}^b$ ) gave a positive peak to  $\text{H}^a$ ,  $\text{H}^d$  &  $\text{CH}_3$

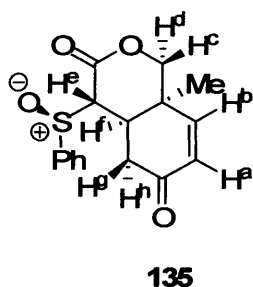
**(*S<sub>SR</sub>*,4*SR*,4*aRS*,8*aSR*)-4-Benzenesulfinyl-8*a*-methyl-1,4*a*,5,8*a*-tetrahydro-4*H*-isochromene-3,6-dione (135):** Off-white solid (82 mg, 7.7 %), m.p. 132 - 134 °C (Found:  $MH^+$  305.0843.  $C_{16}H_{17}SO_4$  requires  $M$ , 305.0842);  $\nu_{max}$  ( $CH_2Cl_2$ )/ $cm^{-1}$  3055, 2985, 1724, 1686, 1424, 1265, 1050, 738;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 7.61 - 7.50 (5 H, m, 5  $\times$  aromatic CH), 6.54 (1 H, dd,  $J$  10.3, 1.8,  $CH=CH-C=O$ ), 6.03 (1 H, d,  $J$  10.3,  $CH=CH-C=O$ ), 3.86 (1 H, d,  $J$  5.6, CH-SO), 3.75 (1 H, d,  $J$  11.3, one of O- $CH_2$ ), 2.90 - 2.84 (3 H, m, one of O- $CH_2$ , ring junction CH & one of  $CH_2-C=O$ ), 2.47 (1 H, dd, 18.7, 4.0, one of  $CH_2-C=O$ ), 1.09 (3 H, s,  $CH_3$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 195.2 (C=O), 163.6 (O-C=O), 152.2 ( $CH=CH-C=O$ ), 139.3 ( $C_q-S$ ), 132.7 ( $p$ -aromatic CH), 132.1 ( $CH=CH-C=O$ ), 129.5 (2  $\times$   $o$ -aromatic CH), 125.1 (2  $\times$   $m$ -aromatic CH), 74.5 (O- $CH_2$ ), 66.5 (CH-SO), 40.6 ( $CH_2-C=O$ ), 36.2 ( $C_q$  ring), 36.1 (ring junction CH), 20.7 ( $CH_3$ );  $m/z$  (APCI) 305 ( $MH^+$ , 100 %), 247 (19), 179 (34).

$^1H - ^1H$  COSY experiment showed the following correlations



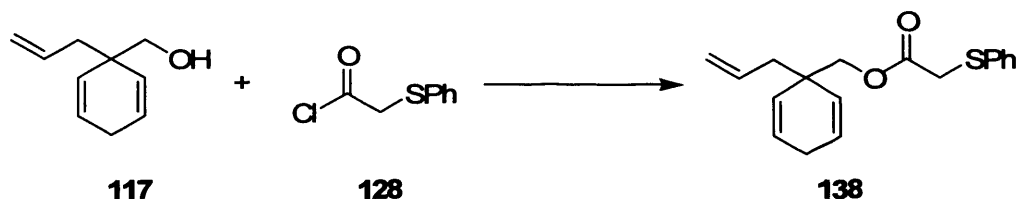
$H^b$ ,  $\delta = 6.54$ , showed a cross peak to  $H^e$  &  $H^f$   
 $H^e$ ,  $\delta = 6.03$ , showed a cross peak to  $H^b$   
 $H^e$ ,  $\delta = 3.86$ , showed a cross peak to  $H^f$  (one of the protons at  $\delta = 2.90 - 2.84$ )  
 $H^e$ ,  $\delta = 2.47$ , showed a cross peak to  $H^i$  (one of the protons at  $\delta = 2.90 - 2.84$ )  
 $H^f$ ,  $H^e$  &  $H^i$ ,  $\delta = 2.90 - 2.84$ , showed a cross peak to  $H^e$ ,  $H^d$  &  $H^g$   
 $H^d$ ,  $\delta = 3.75$ , showed a cross peak to  $H^e$  (one of the protons at  $\delta = 2.90 - 2.84$ )

nOe experiment showed the following enhancements



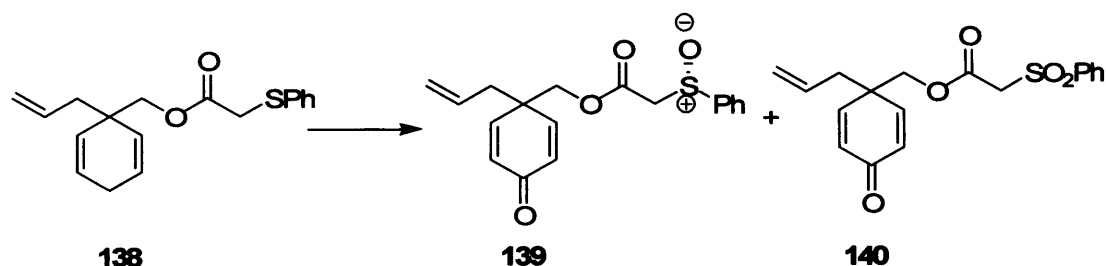
Irradiation point at  $\delta = 1.09$  ( $CH_3$ ) gave positive peak to  $H^b$ ,  $H^d$  & group of protons at  $\delta = 2.90-2.84$   
Irradiation point at  $\delta = 2.47$  ( $H^e$ ) gave positive peak to  $H^e$  & group of protons at  $\delta = 2.90-2.84$   
Irradiation point at  $\delta = 6.54$  ( $H^b$ ) gave positive peak to  $H^e$  &  $CH_3$

**Phenylsulfanylacetic acid 1-allylcyclohexa-2,5-dienylmethyl ester (138)**



2-Phenylsulfanylacetyl chloride **128** (7.6 g, 40.9 mmol, 1.02 equiv.) dissolved in dry  $\text{CH}_2\text{Cl}_2$  (30 ml) was added to a solution of alcohol **117** (6 g, 40 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (330 ml). Triethylamine (8.3 ml, 6 g, 59.5 mmol, 1.5 equiv.) and DMAP (few crystals) were added. The resulting mixture was stirred at room temperature for 13 days and then quenched with aqueous 2 M HCl solution (30 ml). The organic material was extracted into  $\text{CH}_2\text{Cl}_2$  (3  $\times$  50 ml) and dried over  $\text{MgSO}_4$ . After the solvent was removed under reduced pressure, the remaining dark brown oil was purified by flash chromatography (eluting with ether-hexane 2.5:7.5) to afford the *title compound* **138** (5.5 g, 46 %) as a yellow oil;  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3019, 2976, 2886, 1734, 1638, 1584, 1440, 1407, 1277, 1129, 912, 736;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.43 - 7.38 (2 H, m, 2  $\times$  *o*-aromatic CH), 7.35 - 7.27 (2 H, m, 2  $\times$  *m*-aromatic CH), 7.24 (1 H, app. tt,  $J$  7.2, 1.3, *p*-aromatic CH), 5.84 (2 H, app. dt,  $J$  10.4, 3.4, 2  $\times$   $\text{CH}=\text{CH}-\text{CH}_2$ ), 5.63 (1 H, app. ddt,  $J$  18.4, 10.3, 7.2,  $\text{CH}=\text{CH}_2$ ), 5.42 (2 H, app. dt,  $J$  10.4, 2.0, 2  $\times$   $\text{CH}=\text{CH}-\text{CH}_2$ ), 5.06 - 4.97 (2 H, m,  $\text{CH}_2=\text{CH}$ ), 3.97 (2 H, s, O- $\text{CH}_2$ ), 3.67 (2 H, s,  $\text{CH}_2$ -S), 2.63 - 2.58 (2 H, m, ring  $\text{CH}_2$ ), 2.11 (2 H, d,  $J$  7.1,  $\text{CH}_2=\text{CH}-\text{CH}_2$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 169.7 (C=O), 135.2 ( $\text{C}_q$ -S), 134.0 (allyl  $\text{CH}=\text{CH}_2$ ), 129.5 (2  $\times$  alkene CH), 129.1 (2  $\times$  alkene or *o*-aromatic CH), 128.7 (2  $\times$  alkene or *o*-aromatic CH), 126.8 (*p*-aromatic CH), 126.4 (2  $\times$  *m*-aromatic CH), 117.5 ( $\text{CH}_2=\text{CH}$ ), 71.2 (O- $\text{CH}_2$ ), 42.1 ( $=\text{CH}-\text{CH}_2-\text{C}_q$ ), 40.3 ( $\text{C}_q$  ring), 36.5 ( $\text{CH}_2$ -S), 26.6 (ring  $\text{CH}_2$ );  $m/z$  (APCI) 317 ( $\text{MH}^+ + \text{O}$ , 39 %), 315 (24), 275 (17), 149 (15), 133 (100), 123 (92).

**Oxidation of phenylsulfanylacetic acid 1-allylcyclohexa-2,5-dienylmethyl ester (138)**



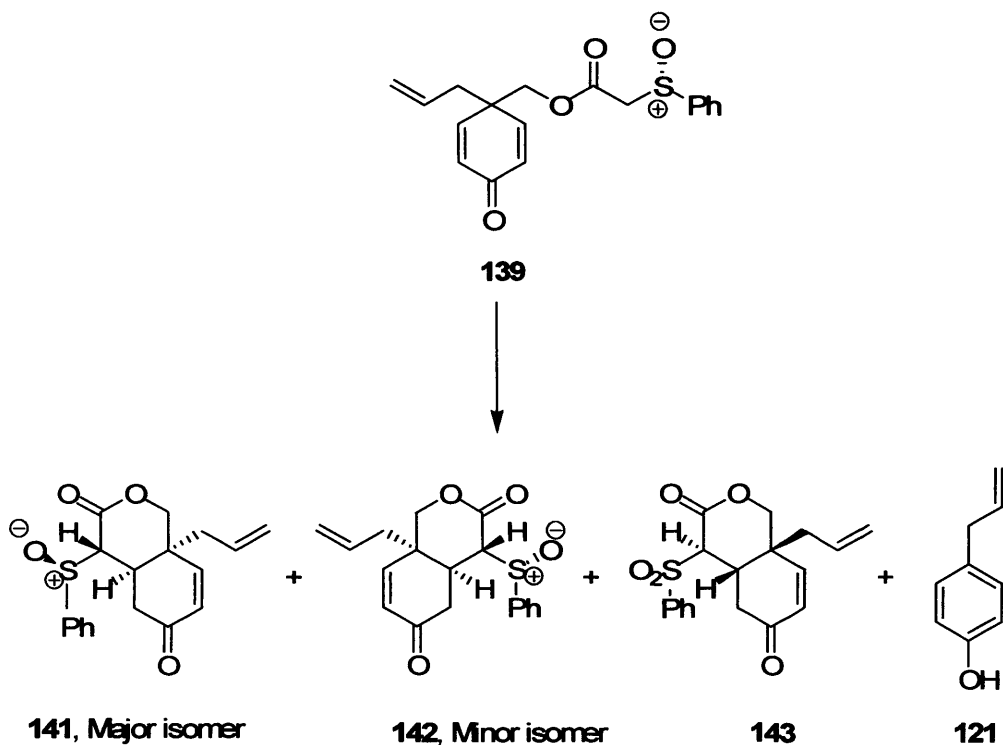
Celite (6.9 g) was added to a suspension of sulfide ester **138** (1.2 g, 4.0 mmol) in dry benzene (55 ml) at 0 °C in a flame dried flask. 5 - 6 M *t*-BuOOH in decane (3.4 ml, 17 mmol, 4.2 equiv.) was added followed by portion-wise addition of pyridinium dichromate (6.3 g, 16.7 mmol, 4.2 equiv.) over 1 hour. After the addition was complete, the reaction mixture was stirred at that temperature for a further 2 hours then the cooling bath was removed and stirring was continued at room temperature for 18 hours. Ethyl acetate was added and the mixture was filtered over basic alumina type H and concentrated *in vacuo* to afford a brown viscous oil. Purification of the remaining oil by flash column chromatography (eluting with petroleum ether-ethyl acetate 2:1.2) afforded compounds **139** and **140**.

**Benzenesulfinylacetic acid 1-allyl-4-oxocyclohexa-2,5-dienylmethyl ester (139):**

Very viscous yellow oil (300 mg, 23 %) (Found:  $MH^+$  331.1004.  $C_{18}H_{19}SO_4$  requires  $M$ , 331.0999);  $\nu_{max}$  (neat)/ $cm^{-1}$  3061, 2923, 1738, 1666, 1627, 1444, 1403, 1261, 1049, 862, 732, 691;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 7.62 - 7.55 (2 H, m, 2  $\times$  aromatic CH), 7.50 - 7.45 (3 H, m, 3  $\times$  aromatic CH), 6.69 - 6.63 (2 H, m, 2  $\times$   $\underline{CH=CH-C=O}$ ), 6.31 - 6.25 (2 H, m, 2  $\times$   $\underline{CH=CH-C=O}$ ), 5.46 (1 H, app. ddt,  $J$  17.7, 10.3, 7.4,  $\underline{CH=CH_2}$ ), 5.07 - 4.98 (2 H, m,  $\underline{CH_2=CH}$ ), 4.17 (1 H, d,  $J$  10.9, one of O- $\underline{CH_2}$ ), 4.07 (1 H, d,  $J$  10.9, one of O- $\underline{CH_2}$ ), 3.70 (1 H, d,  $J$  13.7, one of  $\underline{CH_2-SO}$ ), 3.59 (1 H, d,  $J$  13.7, one of  $\underline{CH_2-SO}$ ), 2.31 (2 H, d,  $J$  7.4,  $\underline{CH_2=CH-CH_2}$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 185.6 (C=O), 164.4 (O-C=O), 149.8 ( $\underline{CH=CH-C=O}$ ), 149.7 ( $\underline{CH=CH-C=O}$ ), 142.8 ( $C_q-S$ ), 131.9 (*p*-aromatic CH), 131.4 ( $\underline{CH=CH-C=O}$ ), 131.4 ( $\underline{CH=CH-C=O}$ ), 130.7 ( $\underline{CH=CH_2}$ ), 129.6 (2  $\times$  *o*-aromatic CH), 124.1 (2  $\times$  *m*-aromatic CH), 120.1 ( $\underline{CH_2=CH}$ ), 68.6 (O- $\underline{CH_2}$ ), 61.3 ( $\underline{CH_2-SO}$ ), 45.3 ( $C_q$  ring), 39.7 ( $=\underline{CH-CH_2-C_q}$ );  $m/z$  (APCI) 331 ( $MH^+$ , 77 %), 195 (32), 185 (16), 147 (100).

**Benzenesulfonylacetic acid 1-allyl-4-oxocyclohexa-2,5-dienylmethyl ester (140):**

Viscous yellow oil (47 mg, 3.4 %);  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.68 - 7.37 (5 H, m, 5  $\times$  aromatic CH), 6.66 (2 H, d,  $J$  10.2, 2  $\times$   $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 6.26 (2 H, d,  $J$  10.2, 2  $\times$   $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 5.53 - 5.40 (1 H, m,  $\text{CH}=\text{CH}_2$ ), 5.08 - 4.92 (2 H, m,  $\text{CH}_2=\text{CH}$ ), 4.11 (2 H, s,  $\text{O}-\text{CH}_2$ ), 4.04 (2 H, s,  $\text{CH}_2-\text{SO}_2$ ), 2.33 (2 H, d,  $J$  7.4,  $\text{CH}_2=\text{CH}-\text{CH}_2$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 185.6 ( $\text{C}=\text{O}$ ), 161.9 ( $\text{O}-\text{C}=\text{O}$ ), 149.6 (2  $\times$   $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 138.6 ( $\text{C}_q-\text{S}$ ), 134.6 ( $p$ -aromatic CH), 131.4 (2  $\times$   $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 130.7 ( $\text{CH}=\text{CH}_2$ ), 129.5 (2  $\times$   $o$ -aromatic CH), 128.4 (2  $\times$   $m$ -aromatic CH), 120.2 ( $\text{CH}_2=\text{CH}$ ), 67.0 ( $\text{O}-\text{CH}_2$ ), 60.7 ( $\text{CH}_2-\text{SO}_2$ ), 45.2 ( $\text{C}_q$  ring), 39.6 ( $=\text{CH}-\text{CH}_2-\text{C}_q$ ).

**Cyclisation of sulfoxide 139**

In a flame-dried flask and under a nitrogen atmosphere, potassium *t*-butoxide (3.3 mmol, 368 mg, 2 equiv.) was added to a cooled solution of sulfoxide dienone 139 (541 mg, 1.64 mmol) in dry THF (60 ml) at 0 °C. The mixture was stirred at this temperature for 3.5 hours, then at room temperature for 14 hours. The resulting mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  solution (20 ml) and the organic material was extracted into  $\text{CH}_2\text{Cl}_2$  (3  $\times$  30 ml). The combined extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to afford 468 mg of a crude mixture of

compounds **121**, **141**, **142**, and **143**, as a golden yellow solid. Purification by flash chromatography (eluting with CH<sub>2</sub>Cl<sub>2</sub>-ethyl acetate 9.3:0.7) afforded the pure products in order as follows:

**4-Allyl phenol (121)**: Yellow oil (21 mg, 9.6 %). Data as previously reported (page 163).

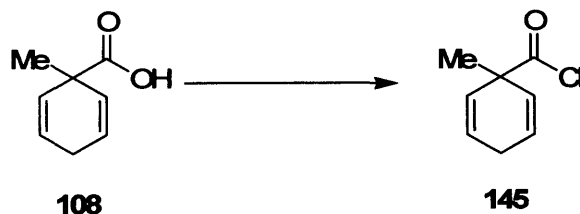
**(4*RS*,4*aSR*,8*aRS*)-4-Benzenesulfonyl-8*a*-allyl-1,4*a*,5,8*a*-tetrahydro-4*H*-isochromene-3,6-dione (143)**: Off-white solid (23 mg, 4.0 %), m.p. 159 - 161°C (Found: MNH<sub>4</sub><sup>+</sup> 364.1215. C<sub>18</sub>H<sub>22</sub>O<sub>5</sub>NS requires M, 364.1213);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3055, 2986, 1743, 1683, 1448, 1421, 1400, 1324, 1265, 1150, 1083, 931, 896, 817, 738;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.82 - 7.78 (2 H, m, 2 × *o*-aromatic CH), 7.66 (1 H, app. tt, *J* 7.4, 1.2, *p*-aromatic CH), 7.53 (2 H, app. t, *J* 7.8, 2 × *m*-aromatic CH), 6.65 (1 H, dd, *J* 10.4, 2.0, CH=CH-C=O), 6.09 (1 H, d, *J* 10.4, CH=CH-C=O), 5.75 (1 H, app. ddt, *J* 17.1, 10.1, 7.6, CH=CH<sub>2</sub>), 5.28 - 5.18 (2 H, m, CH<sub>2</sub>=CH), 4.52 (1 H, d, *J* 11.4, one of O-CH<sub>2</sub>), 4.25 (1 H, d, *J* 11.4, one of O-CH<sub>2</sub>), 3.72 (1 H, d, *J* 5.1, CH-SO<sub>2</sub>), 3.44 (1 H, app. tt, *J* 5.1, 2.4, ring junction CH), 2.97 (1 H, dd, *J* 17.7, 5.1, one of CH<sub>2</sub>-C=O), 2.60 - 2.45 (2 H, m, one of CH<sub>2</sub>-C=O & one of CH<sub>2</sub>=CH-CH<sub>2</sub>), 2.37 (1 H, dd, *J* 14.3, 7.9, one of CH<sub>2</sub>=CH-CH<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 194.8 (C=O), 162.4 (O-C=O), 151.2 (CH=CH-C=O), 136.1 (C<sub>q</sub>-S), 135.0 (*p*-aromatic CH), 132.6 (CH=CH-C=O), 130.3 (CH<sub>2</sub>=CH), 129.3 (2 × *o*-aromatic CH), 129.3 (2 × *m*-aromatic CH), 121.5 (CH<sub>2</sub>=CH), 73.7 (O-CH<sub>2</sub>), 69.9 (CH-SO<sub>2</sub>), 40.5 (CH<sub>2</sub>-C=O), 39.7 (=CH-CH<sub>2</sub>-C<sub>q</sub>), 36.9 (C<sub>q</sub> ring), 36.7 (ring junction CH); *m/z* (APCI) 347 (MH<sup>+</sup>, 100 %), 147 (14).

**(S<sub>SR</sub>,4*RS*,4*aSR*,8*aRS*)-4-Benzenesulfinyl-8*a*-allyl-1,4*a*,5,8*a*-tetrahydro-4*H*-isochromene-3,6-dione (142)**: White solid (82 mg, 15.2 %), m.p. 126 - 128 °C (Found: MNH<sub>4</sub><sup>+</sup> 348.1268. C<sub>18</sub>H<sub>22</sub>O<sub>4</sub>NS requires M, 348.1264);  $\nu_{\max}$  (CDCl<sub>3</sub>)/cm<sup>-1</sup> 3066, 2905, 1732, 1682, 1444, 1400, 1222, 1085, 1051, 749, 691;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.61 - 7.50 (5 H, m, 5 × aromatic CH), 6.65 (1 H, dd, *J* 10.2, 1.8, CH=CH-C=O), 6.04 (1 H, d, *J* 10.2, CH=CH-C=O), 5.73 (1 H, dddd, *J* 16.8, 10.4, 8.1, 7.0, CH=CH<sub>2</sub>), 5.26 (1 H, app. d, *J* 10.4, one of CH<sub>2</sub>=CH), 5.15 (1 H, dd, *J* 16.8, 1.3, one of CH<sub>2</sub>=CH), 4.37 (1 H, d, *J* 11.2, one of O-CH<sub>2</sub>), 4.15 (1 H, d, *J* 11.2, one

of O-CH<sub>2</sub>), 3.23 (1 H, d, *J* 4.9, CH-SO), 3.03 (1 H, app. tt, *J* 4.9, 2.7, ring junction CH), 2.45 (1 H, dd, *J* 14.1, 7.0, one of CH<sub>2</sub>=CH-CH<sub>2</sub>), 2.37 (1 H, dd, *J* 17.5, 5.4 one of CH<sub>2</sub>-C=O), 2.29 (1 H, dd, *J* 14.1, 8.1, one of CH<sub>2</sub>=CH-CH<sub>2</sub>), 0.95 (1 H, dd, *J* 17.5, 2.7, one of CH<sub>2</sub>-C=O);  $\delta_C$  (100 MHz; CDCl<sub>3</sub>) 194.9 (C=O), 167.0 (O-C=O), 151.9 (CH=CH-C=O), 140.2 (C<sub>q</sub>-S), 132.3 (*p*-aromatic CH & CH=CH<sub>2</sub>), 130.7 (CH=CH-C=O), 129.8 (2 × *o*-aromatic CH), 124.0 (2 × *m*-aromatic CH), 121.1 (CH<sub>2</sub>=CH), 73.1 (O-CH<sub>2</sub>), 69.5 (CH-SO), 39.9 (CH<sub>2</sub>-C=O), 39.5 (=CH-CH<sub>2</sub>-C<sub>q</sub>), 39.2 (C<sub>q</sub> ring), 32.1 (ring junction CH); *m/z* (APCI) 331 (MH<sup>+</sup>, 13 %), 237 (10), 236 (20), 235 (100), 205 (42), 187 (9), 159 (13), 123 (9).

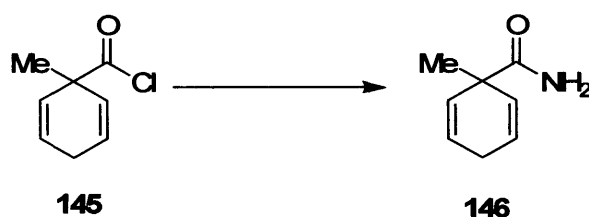
**(S<sub>SR</sub>,4S<sub>R</sub>,4aR<sub>S</sub>,8aS<sub>R</sub>)-4-Benzenesulfinyl-8a-allyl-1,4a,5,8a-tetrahydro-4H-  
isochromene-3,6-dione (141):** White crystalline solid (84 mg, 15.5 %), m.p. 111 - 113 °C (Found: MNH<sub>4</sub><sup>+</sup> 348.1266. C<sub>18</sub>H<sub>22</sub>O<sub>4</sub>NS requires M, 348.1264);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3065, 2913, 1714, 1683, 1401, 1222, 1167, 1054, 754, 692;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 7.60 - 7.49 (5 H, m, 5 × aromatic CH), 6.56 (1 H, dd, *J* 10.2, 2.0, CH=CH-C=O), 6.07 (1 H, d, *J* 10.2, CH=CH-C=O), 5.50 (1 H, dddd, *J* 16.8, 9.9, 8.1, 7.1, CH=CH<sub>2</sub>), 5.15 (1 H, app. d, *J* 9.9, one of CH<sub>2</sub>=CH), 5.07 (1 H, dd, *J* 16.8, 1.2, one of CH<sub>2</sub>=CH), 3.88 (1 H, d, *J* 5.8, CH-SO), 3.80 (1 H, d, *J* 11.4, one of O-CH<sub>2</sub>), 3.01 (1 H, app. tt, *J* 5.3, 2.4, ring junction CH), 2.88 (1 H, dd, *J* 17.7, 5.0, one of CH<sub>2</sub>-C=O), 2.85 (1 H, d, *J* 11.4, one of O-CH<sub>2</sub>), 2.44 (1 H, dd, *J* 17.7, 2.2, one of CH<sub>2</sub>-C=O), 2.31 (1 H, dd, *J* 14.2, 7.1, CH<sub>2</sub>=CH-CH<sub>2</sub>), 2.15 (1 H, dd, *J* 14.2, 8.1, one of CH<sub>2</sub>=CH-CH<sub>2</sub>);  $\delta_C$  (100 MHz; CDCl<sub>3</sub>) 195.2 (ring C=O), 163.6 (O-C=O), 151.6 (CH=CH-C=O), 139.2 (C<sub>q</sub>-S), 132.7 (*p*-aromatic CH), 132.6 (CH<sub>2</sub>=CH), 130.3 (CH=CH-C=O), 129.4 (2 × *o*-aromatic CH), 125.2 (2 × *m*-aromatic CH), 121.2 (CH<sub>2</sub>=CH), 73.0 (O-CH<sub>2</sub>), 66.5 (CH-SO), 40.6 (CH<sub>2</sub>-C=O), 39.4 (=CH-CH<sub>2</sub>-C<sub>q</sub>), 38.8 (C<sub>q</sub> ring), 33.7 (ring junction CH); *m/z* (APCI) 331 (MH<sup>+</sup>, 100 %), 205 (38), 159 (24).

### 1-Methyl-cyclohexa-2,5-dienecarbonyl chloride (**145**)<sup>31</sup>



Thionyl chloride (20 ml) was added to 1-methylcyclohexa-2,5-dienecarboxylic acid **108** (8.8 g, 63.8 mmol) and the mixture was heated under reflux at 70 °C for 2 hours. The excess thionyl chloride was removed *in vacuo* at 60 °C to afford the *title compound* (9 gm, 90 %) as an essentially-pure brown oil which used without further purification;  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3034, 2980, 2875, 1785, 1451, 904, 786, 710;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 5.90 (2 H, app. dt, *J* 10.3, 3.5, 2 × CH=CH-CH<sub>2</sub>), 5.63 (2 H, app. dt, *J* 10.3, 2.0, 2 × CH=CH-CH<sub>2</sub>), 2.73 - 2.56 (2 H, m, ring CH<sub>2</sub>), 1.36 (3 H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 182.1 (C=O), 128.1 (2 × alkene CH), 125.0 (2 × alkene CH), 43.7 (C<sub>q</sub> ring), 27.3 (CH<sub>3</sub>), 25.9 (ring CH<sub>2</sub>).

### 1-Methyl-cyclohexa-2,5-dienecarboxylic acid amide (**146**)

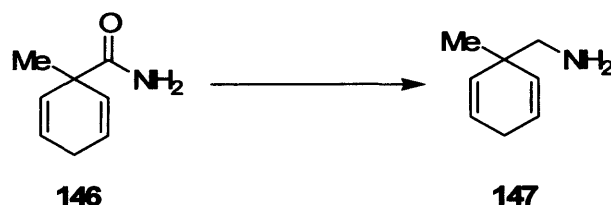


Liquid ammonia (100 ml) was condensed *via* a cold-finger condenser into a solution of acid chloride **145** (1.0 g, 6.4 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 ml) at -78 °C. After being stirred for 1.5 hour at this temperature, the cooling bath was removed and the ammonia was allowed to evaporate overnight. The remaining yellow residue was dissolved in water (200 ml) and the product was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 ml). The combined extracts were dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to give the *title amide* **146** (780 mg, 89 %) as an essentially-pure yellow oil which then solidified into a pale yellow waxy solid, m.p. 52 - 54 °C;  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3474, 3338, 3197, 3027, 2969, 2928, 2871, 1666, 1596, 1368;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>)



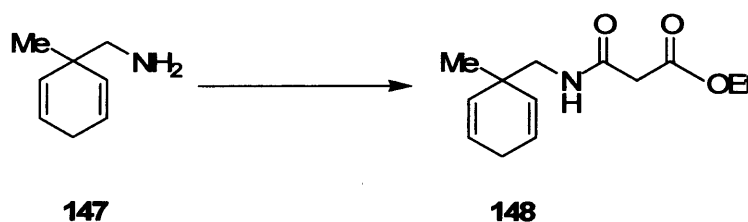
5.84 (2 H, app. dt,  $J$  10.3, 3.3,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 5.68 (2 H, app. dt,  $J$  10.3, 1.8,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 2.70 – 2.66 (2 H, m, ring  $\text{CH}_2$ ), 1.27 (3 H, s,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 178.2 ( $\text{C}=\text{O}$ ), 129.8 ( $2 \times$  alkene CH), 125.1 ( $2 \times$  alkene CH), 44.5 ( $\text{C}_q$  ring), 25.9 (ring  $\text{CH}_2$ ), 25.4 ( $\text{CH}_3$ ).

**C-(1-Methylcyclohexa-2,5-dienyl)-methylaniline (147)**



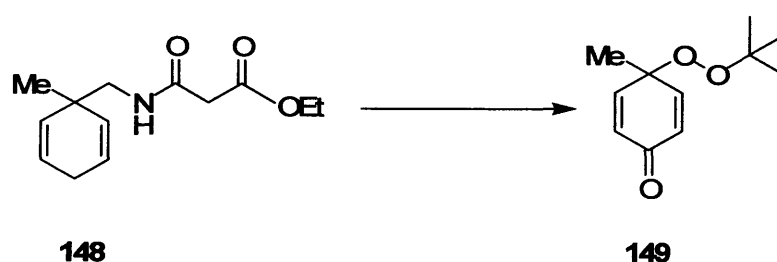
To a stirred suspension of  $\text{LiAlH}_4$  (10.1 g, 266 mmol) in dry THF (230 ml) under a nitrogen atmosphere at room temperature was added a solution of amide **146** (6.1 g, 45.5 mmol) in dry THF (15 ml). After being stirred at room temperature for 2 hours, the reaction mixture was refluxed for 17 hours and then cooled to room temperature. 15 % Aqueous NaOH solution (10.1 ml) was added carefully followed by water (30.4 ml) and stirring was continued at room temperature for a further 72 hours. Filtration and concentration under reduced pressure afforded the *title amine* **147** (4.5 g, 82 %) as an essentially-pure yellow oil;  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3282, 3014, 2921, 1648, 1456, 1367, 946, 731;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.79 (2 H, app. dt,  $J$  10.4, 3.4,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 5.27 (2 H, app. dt,  $J$  10.4, 2.0,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 2.59 – 2.50 (2 H, m, ring  $\text{CH}_2$ ), 2.34 (2 H, s,  $\text{CH}_2\text{-N}$ ), 1.30 (2 H, broad s,  $\text{NH}_2$ ), 0.91 (3 H, s,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 131.8 ( $2 \times$  alkene CH), 125.8 ( $2 \times$  alkene CH), 52.6 ( $\text{N}-\text{CH}_2$ ), 39.4 (ring  $\text{C}_q$ ), 26.6 ( $\text{CH}_3$ ), 26.5 (ring  $\text{CH}_2$ ).

**N-(1-Methylcyclohexa-2,5-dienylmethyl)-malonamic acid ethyl ester (148)**



Ethyl malonyl chloride (5.2 ml, 41.2 mmol, 1.1 equiv.) dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (10 ml) was added to a solution of the amine **147** (4.5 g, 36.6 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (50 ml). Triethylamine (0.99 g, 1.4 ml, 9.8 mmol) and DMAP (few crystals) were added. The resulting mixture was stirred at room temperature for 66 hours, then quenched with aqueous 2 M HCl solution (30 ml). The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 50) and dried over MgSO<sub>4</sub>. The combined extracts were concentrated under reduced pressure to give a yellow oil which was purified by Kugelrohr distillation (b.p. 182 - 194 °C at 0.6 mm Hg) to afford the *title amidoester* **148** (4.6 g, 54 %) as a pale yellow oil (Found: MH<sup>+</sup> 238.1435. C<sub>13</sub>H<sub>20</sub>O<sub>3</sub>N requires M, 238.1438);  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3312, 3015, 2964, 2926, 2870, 1740, 1648, 1555, 1456, 1033, 945;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.08 (1 H, broad s, NH), 5.77 (2 H, app. dt, *J* 10.3, 3.0, 2 × CH=CH-CH<sub>2</sub>), 5.35 (2 H, app. dt, *J* 10.3, 1.9, 2 × CH=CH-CH<sub>2</sub>), 4.10 (2 H, q, *J* 7.0, O-CH<sub>2</sub>-CH<sub>3</sub>), 3.19 (2 H, s, O=C-CH<sub>2</sub>-C=O), 3.07 (2 H, d, *J* 5.5, CH<sub>2</sub>-NH), 2.64 - 2.48 (2 H, m, ring CH<sub>2</sub>), 1.20 (3 H, t, *J* 7.0, CH<sub>3</sub>-CH<sub>2</sub>), 1.00 (3 H, s, CH<sub>3</sub>-C<sub>q</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 169.5 (O-C=O), 164.9 (HN-C=O) 131.1 (2 × alkene CH), 125.5 (2 × alkene CH), 61.3 (O-CH<sub>2</sub>), 49.1 (CH<sub>2</sub>-NH), 41.1 (O=C-CH<sub>2</sub>-C=O), 37.1 (C<sub>q</sub> ring), 26.5 (CH<sub>3</sub>-CH<sub>2</sub>), 26.1 (ring CH<sub>2</sub>), 14.0 (CH<sub>3</sub>-C<sub>q</sub>); *m/z* (APCI) 238 (M<sup>+</sup>, 100 %), 144 (14), 132 (13).

#### 4-*tert*-Butylperoxy-4-methyl-cyclohexa-2,5-dienone (**64**)<sup>41</sup>

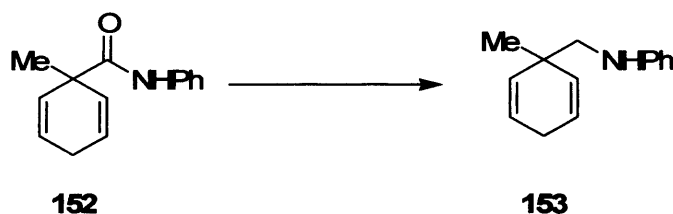


Celite (8.2 g) was added to a suspension of amidoester **148** (1.6 g, 6.7 mmol) in dry benzene (50 ml) at 0 °C in a flame-dried flask. 5 - 6 M *t*-BuOOH in decane (5.3 ml, 26.5 mmol, 4 equiv.) was added followed by portion-wise addition of pyridinium dichromate (10.1 g, 26.8 mmol, 4 equiv.) over 10 min. After the addition was completed, the cooling bath was removed and the reaction mixture was stirred at room temperature for 24 hours. Dichloromethane was added and the mixture was



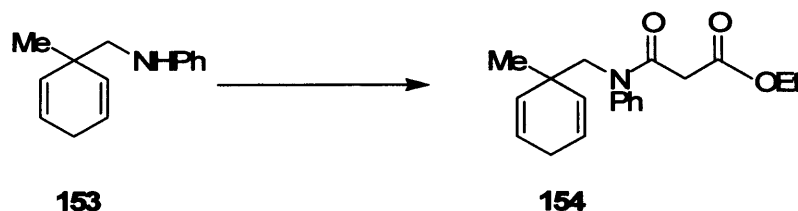
*m*-aromatic CH), 45.9 (ring C<sub>q</sub>), 26.0 (ring CH<sub>2</sub>), 25.1 (CH<sub>3</sub>); *m/z* (APCI) 214 (MH<sup>+</sup>, 100 %).

**(1-Methylcyclohexa-2,5-dienylmethyl)-phenylamine (153)**



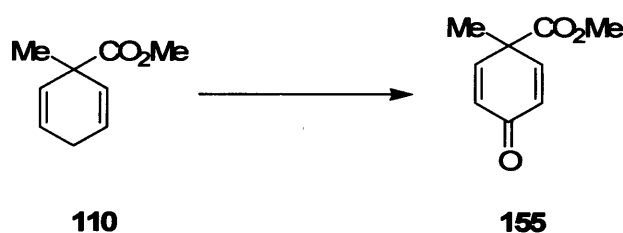
To a stirred suspension of LiAlH<sub>4</sub> (4.3 g, 113.3 mmol) in dry THF (90 ml) under a nitrogen atmosphere at room temperature in a flame-dried flask was added carefully a solution of amide **152** (4 g, 18.9 mmol) in dry THF (20 ml). After being stirred at room temperature for four days, the reaction mixture was refluxed for 6.5 hours then stirred at room temperature for further 17 hours. 15 % Aqueous NaOH solution (4.3 ml) was added carefully followed by water (12.9 ml) and the stirring was continued at room temperature for three hours. Filtration and concentration under reduced pressure afforded the *title amine* **153** (3.0 g, 81 %) as an essentially-pure oil (Found: MH<sup>+</sup> 200.1434. C<sub>14</sub>H<sub>18</sub>N requires M, 200.1436);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3402, 3011, 2964, 2862, 2816, 1603, 1504, 1319, 1253;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) (spectrum showed significant broadening) 7.11 - 6.99 (2 H, m, 2 × *o*-aromatic CH), 6.60 - 6.52 (1 H, m, *p*-aromatic CH), 6.50 - 6.43 (2 H, m, 2 × *m*-aromatic CH), 5.80 - 5.71 (2 H, m, 2 × CH=CH-CH<sub>2</sub>), 5.37 (2 H, app. d, *J* 8.9, 2 × CH=CH-CH<sub>2</sub>), 3.46 (1 H, broad s, NH), 2.82 (2 H, s, CH<sub>2</sub>-NH), 2.57 (2 H, app. broad s, ring CH<sub>2</sub>), 1.04 (3 H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 148.8 (aromatic C<sub>q</sub>), 132.2 (2 × alkene CH), 129.3 (2 × alkene CH), 125.4 (2 × *o*-aromatic CH), 117.1 (*p*-aromatic CH), 112.9 (2 × *m*-aromatic CH), 54.3 (CH<sub>2</sub>-NH), 37.3 (ring C<sub>q</sub>), 27.5 (CH<sub>3</sub>), 26.4 (ring CH<sub>2</sub>); *m/z* (APCI) 201 (14 %), 200 (MH<sup>+</sup>, 100).

***N*-(1-Methylcyclohexa-2,5-dienylmethyl)-*N*-phenyl-malonamic acid ethyl ester (154)**



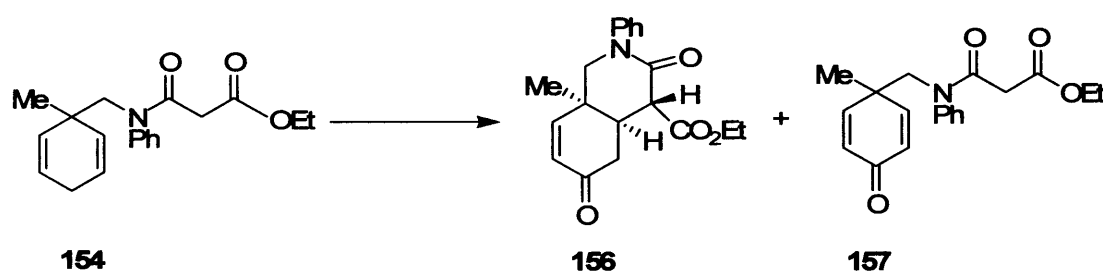
Ethyl malonyl chloride (0.96 ml, 7.5 mmol, 1 equiv.) dissolved in (5 ml) dry  $\text{CH}_2\text{Cl}_2$  was added to a solution of amine **153** (1.5 g, 7.5 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (30 ml). Triethylamine (0.8 g, 1.1 ml, 8.3 mmol, 1.1 equiv.) and DMAP (few crystals) were added and the resulting mixture was stirred at room temperature for 24 hours. The reaction was quenched with aqueous 2 M HCl solution (30 ml) and the organic material was extracted into  $\text{CH}_2\text{Cl}_2$  (3 x 25 ml). The combined extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to afford the *title amidoester* **154** (2.2 g, 95 %) as an essentially-pure viscous brown oil (Found:  $\text{MH}^+$  314.1752.  $\text{C}_{19}\text{H}_{24}\text{NO}_3$  requires M, 314.1751);  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3015, 2978, 2870, 1740, 1662, 1595, 1484, 1394, 1322, 1242, 1153;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.27 - 7.18 (3 H, m, 3  $\times$  aromatic CH), 7.08 (2 H, app. dd,  $J$  8.0, 1.5, 2  $\times$  aromatic CH), 5.46 (2 H, app. dt,  $J$  10.4, 3.4, 2  $\times$   $\text{CH}=\text{CH}-\text{CH}_2$ ), 5.28 (2 H, app. dt,  $J$  10.4, 2.0, 2  $\times$   $\text{CH}=\text{CH}-\text{CH}_2$ ), 4.03 (2 H, q,  $J$  7.2,  $\text{O}-\text{CH}_2-\text{CH}_3$ ), 3.74 (2 H, s,  $\text{CH}_2-\text{NPh}$ ), 3.10 (2 H, s,  $\text{O}=\text{C}-\text{CH}_2-\text{C}=\text{O}$ ), 2.49 - 2.45 (2 H, m, ring  $\text{CH}_2$ ), 1.15 (3 H, t,  $J$  7.2,  $\text{CH}_3-\text{CH}_2$ ), 0.96 (3 H, s,  $\text{CH}_3-\text{C}_q$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 167.9 ( $\text{O}-\text{C}=\text{O}$ ), 166.7 ( $\text{N}-\text{C}=\text{O}$ ), 143.0 (aromatic  $\text{C}_q$ ), 132.6 (2  $\times$  alkene CH), 129.1 (2  $\times$  alkene CH), 128.5 (2  $\times$  *o*-aromatic CH), 127.8 (*p*-aromatic CH), 123.4 (2  $\times$  *m*-aromatic CH), 61.2 ( $\text{O}-\text{CH}_2$ ), 58.5 ( $\text{CH}_2-\text{NPh}$ ), 42.0 ( $\text{O}=\text{C}-\text{CH}_2-\text{C}=\text{O}$ ), 38.8 (ring  $\text{C}_q$ ), 28.0 ( $\text{CH}_3-\text{CH}_2$ ), 26.1 (ring  $\text{CH}_2$ ), 14.1 ( $\text{CH}_3-\text{C}_q$ );  $m/z$  (APCI) 314 ( $\text{MH}^+$ , 100%).

**1-Methyl-4-oxocyclohexa-2,5-dienecarboxylic acid methyl ester (155)**



Pyridinium dichromate (1.2 g, 3.3 mmol, 5 equiv) and dry 4 Å molecular sieves (1.0 g) were added to a solution of ester **110** (0.1 g, 0.66 mmol) in ethanol-free chloroform (10 ml). The reaction mixture was heated under reflux for 24 hours, then allowed to cool to room temperature. Ethyl acetate was added and the resulting mixture was filtered through a short pad of florisil. The resulting filtrate was concentrated under reduced pressure to afford the *title compound* (62 mg, 57 %) as an essentially-pure colourless oil;  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 2956, 1736, 1668, 1631, 1453, 1258, 1175, 1117, 859;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.04 (2 H, d,  $J$  9.9, 2 × CH=CH-C=O), 6.28 (2 H, d,  $J$  9.9, 2 × CH=CH-C=O), 3.73 (3 H, s, O-CH<sub>3</sub>), 1.55 (3 H, s, CH<sub>3</sub>-C<sub>q</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 184.9 (C=O), 171.2 (O-C=O), 148.9 (2 × CH=CH-C=O), 129.0 (2 × CH=CH-C=O), 53.2 (O-CH<sub>3</sub>), 48.1 (ring C<sub>q</sub>), 24.9 (CH<sub>3</sub>-C<sub>q</sub>).

#### Allylic oxidation of amidoester **154**



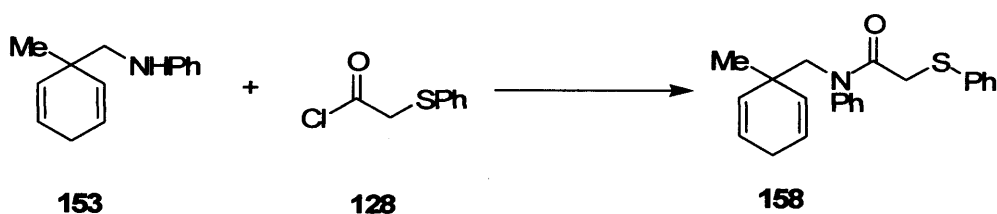
Pyridinium dichromate (2.9 g, 7.8 mmol, 5 equiv) and dry 4 Å molecular sieves (2.4 g) were added to a solution of amidoester **154** (490 mg, 1.6 mmol) in ethanol-free chloroform (40 ml). The reaction mixture was heated under reflux for 3.5 hours, and then allowed to cool to room temperature. Ethyl acetate and CH<sub>2</sub>Cl<sub>2</sub> were added and the resulting mixture was filtered through a short pad of florisil. The resulting filtrate was concentrated under reduced pressure to afford a brown oil. Purification by flash chromatography (eluting with CH<sub>2</sub>Cl<sub>2</sub>-ethyl acetate, 7.5:2.5) afforded the bicyclic enone **156** (16 mg, 3.1%) as a slightly impure yellow oil and amidodienone **157** (35 g, 6.8 %) as a viscous yellow oil respectively.

**(4*RS*,4*aRS*,8*aRS*)-8*a*-Methyl-3,6-dioxo-2-phenyl-1,2,3,4,4*a*,5,6,8*a*-octahydro-isoquinoline-4-carboxylic acid ethyl ester (**156**):** Formed on silica gel during purification of the crude reaction mixture of compound **157** and was isolated as a

slightly impure yellow oil (16 mg, 3.1%);  $\nu_{\max}$  ( $\text{CH}_2\text{Cl}_2$ )/ $\text{cm}^{-1}$  3056, 2976, 735, 1679, 1600, 1494, 1442, 756, 694;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.37 - 7.05 (5 H, m, 5  $\times$  aromatic CH), 6.69 (1 H, dd,  $J$  10.2, 1.8,  $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 6.07 (1 H, d,  $J$  10.2,  $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 4.23 - 4.12 (2 H, m, O- $\text{CH}_2$ ), 3.84 (1 H, d,  $J$  12.7, one of  $\text{CH}_2-\text{N}$ ), 3.51 (1 H, d,  $J$  12.7, one of  $\text{CH}_2-\text{N}$ ), 3.38 (1 H, d,  $J$  7.9,  $\text{CH}-\text{CO}_2\text{Et}$ ), 2.83 - 2.76 (2 H, m, ring junction CH & one of  $\text{CH}_2-\text{C}=\text{O}$ ), 2.43 (1 H, dd,  $J$  18.8, 5.0 one of  $\text{CH}_2-\text{C}=\text{O}$ ), 1.32 (3 H, s,  $\text{CH}_3-\text{C}_q$ ), 1.24 (3 H, t,  $J$  7.1,  $\text{CH}_3-\text{CH}_2$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 195.8 ( $\text{C}=\text{O}$ ), 170.4 (O- $\text{C}=\text{O}$ ), 162.2 ( $\text{N}-\text{C}=\text{O}$ ), 142.1 (aromatic  $\text{C}_q-\text{N}$ ), 153.4 ( $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 130.8 ( $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 129.8 (2  $\times$  *o*-aromatic CH), 127.2 (*p*-aromatic CH), 125.5 (2  $\times$  *m*-aromatic CH), 62.1 (O- $\text{CH}_2$ ), 60.1 ( $\text{CH}_2-\text{N}$ ), 53.2 (O- $\text{C}-\text{CH}-\text{C}=\text{O}$ ), 42.0 (ring junction CH), 39.2 ( $\text{CH}_2-\text{C}=\text{O}$ ), 36.9 (ring  $\text{C}_q$ ), 23.9 ( $\text{CH}_3-\text{CH}_2$ ), 14.1 ( $\text{CH}_3-\text{C}_q$ ).

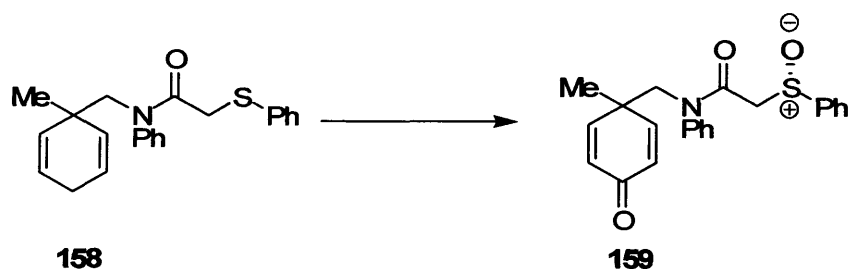
***N*-(1-Methyl-4-oxocyclohexa-2,5-dienylmethyl)-*N*-phenyl-malonamic acid ethyl ester (157):** Viscous yellow oil (35 g, 6.8 %) (Found:  $\text{MH}^+$  328.1550.  $\text{C}_{19}\text{H}_{22}\text{NO}_4$  requires M, 328.1543);  $\nu_{\max}$  (neat)/ $\text{cm}^{-1}$  2979, 2925, 1738, 1662, 1626, 1596, 1393, 1155, 862, 702;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.30 - 7.22 (3 H, m, 3  $\times$  aromatic CH), 7.00 - 6.95 (2 H, m, 2  $\times$  aromatic CH), 6.68 (2 H, d,  $J$  10.1, 2  $\times$   $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 6.08 (2 H, d,  $J$  10.1, 2  $\times$   $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 4.04 (2 H, s,  $\text{CH}_2-\text{N}$ ), 4.02 (2 H, q,  $J$  7.1, O- $\text{CH}_2-\text{CH}_3$ ), 3.05 (2 H, s, O- $\text{C}-\text{CH}_2-\text{C}=\text{O}$ ), 1.18 (3 H, s,  $\text{CH}_3-\text{C}_q$ ), 1.14 (3 H, t,  $J$  7.1,  $\text{CH}_2-\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 186.2 ( $\text{CH}-\text{C}=\text{O}$ ), 167.3 (O- $\text{C}=\text{O}$ ), 166.8 ( $\text{N}-\text{C}=\text{O}$ ), 153.7 (2  $\times$   $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 141.7 ( $\text{C}_q-\text{N}$ ), 129.6 (2  $\times$   $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 129.1 (2  $\times$  aromatic CH), 128.5 (3  $\times$  aromatic CH), 61.4 (O- $\text{CH}_2$ ), 57.0 ( $\text{CH}_2-\text{NPh}$ ), 44.5 ( $\text{C}_q$  ring), 41.7 (O- $\text{C}-\text{CH}_2-\text{C}=\text{O}$ ), 24.2 ( $\text{CH}_3-\text{CH}_2$ ), 14.1 ( $\text{CH}_3-\text{C}_q$ );  $m/z$  (APCI) 328 ( $\text{MH}^+$ , 100 %), 305 (14), 290 (15), 220 (10), 208 (9), 153 (7), 139 (8).

***N*-(1-Methylcyclohexa-2,5-dienylmethyl)-*N*-phenyl-2-phenylsulfanylacetamide (158)**



2-Phenylsulfanylacetyl chloride **128** (4.8 g, 25.7 mmol, 1.02 equiv.) dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (20 ml) was added to a solution of the amine **153** (5 g, 25.1 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (50 ml). Triethylamine (3.8 g, 5.2 ml, 37.3 mmol, 1.5 equiv.) and DMAP (few crystals) were added. The resulting mixture was stirred at room temperature for 72 hours, and then quenched with aqueous 2 M HCl solution (30 ml). The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 ml) and dried over MgSO<sub>4</sub>. The combined extracts were concentrated under reduced pressure to give a brown oil which was purified by flash chromatography (eluting with ethyl acetate-hexane 2:8) to afford the *title phenylsulfanyl amide* **158** (5.4 g, 59 %) as a yellow oil (Found: MH<sup>+</sup> 350.1566. C<sub>22</sub>H<sub>24</sub>NSO requires M, 350.1573);  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3057, 3015, 2965, 2921, 2866, 1654, 1594, 1494, 1389, 1198, 738;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.26 - 7.02 (10 H, m, aromatic CH), 5.45 (2 H, app. dt, *J* 10.4, 3.3, 2 × CH=CH-CH<sub>2</sub>), 5.28 (2 H, app. dt, *J* 10.4, 2.0, 2 × CH=CH-CH<sub>2</sub>), 3.71 (2 H, s, CH<sub>2</sub>-S), 3.42 (2 H, s, CH<sub>2</sub>-NPh), 2.51 - 2.45 (2 H, m, ring CH<sub>2</sub>), 0.94 (3 H, s, CH<sub>3</sub>-C<sub>q</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 169.0 (C=O), 142.9 (aromatic C<sub>q</sub>-N), 135.9 (C<sub>q</sub>-S), 132.6 (2 × alkene CH), 130.3 (2 × alkene CH), 129.1 (2 × aromatic CH), 128.8 (2 × aromatic CH), 128.7 (2 × aromatic CH), 127.8 (*p*-aromatic CH), 126.5 (*p*-aromatic CH), 123.5 (2 × aromatic CH), 58.9 (CH<sub>2</sub>-N), 38.9 (ring C<sub>q</sub>), 7.6 (S-CH<sub>2</sub>), 28.1 (CH<sub>3</sub>-C<sub>q</sub>), 26.2 (ring CH<sub>2</sub>); *m/z* (APCI) 350 (MH<sup>+</sup>, 100 %), 274 (7), 260 (14), 244 (21), 241 (10), 94 (14).

**2-Benzenesulfinyl-N-(1-methyl-4-oxo-cyclohexa-2,5-dienylmethyl)-N-phenylacetamide (159)**

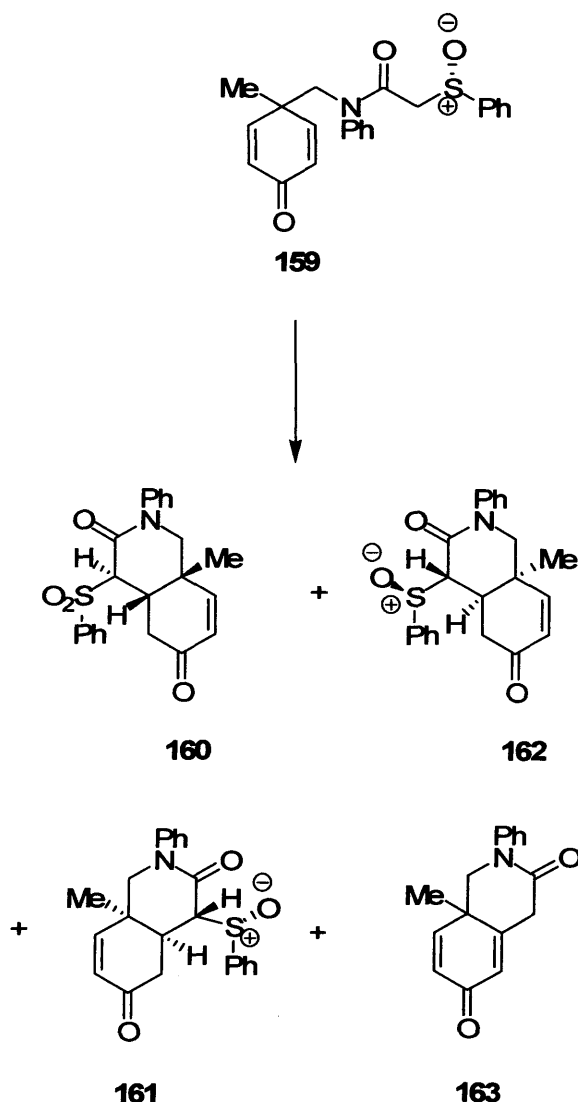


Pyridinium dichromate (8.1 g, 21.6 mmol, 3 equiv.) was added to a cooled solution of sulfide amide **158** (2.5 g, 7.2 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (30 ml) at -20 °C. 70 % *t*-BuOOH in water (3.02 ml, 31.6 mmol, 4.37 equiv.) was added. The resulting mixture was stirred at this temperature for 48 hours, diluted with ethyl acetate, and filtered through a pad of celite / sodium sulfate. The filtrate was concentrated under reduced pressure to afford a brown residue which was purified by flash chromatography



(eluting with ethyl acetate-CH<sub>2</sub>Cl<sub>2</sub> 3:1) to give the *title enone* (0.76 g, 28 %) as a pale brown viscous oil;  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3538, 3357, 1662, 1594, 1494, 1404, 1293, 1131, 1045, 946, 862, 747, 699;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.57 - 7.21 (10 H, m, 10 × aromatic CH), 6.64 - 6.56 (2 H, m, 2 × CH=CH-C=O), 6.06 - 5.98 (2 H, m, 2 × CH=CH-C=O), 3.96 and 3.93 (2 H, AB quartet, *J* 12.0, CH<sub>2</sub>-N), 3.64 (1 H, d, *J* 13.9, one of CH<sub>2</sub>-SO), 3.37 (1 H, d, *J* 13.9, one of CH<sub>2</sub>-SO), 1.16 (3 H, s, CH<sub>3</sub>-C<sub>q</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 185.9 (C=O), 164.9 (N-C=O), 153.4 (CH=CH-C=O), 153.3 (CH=CH-C=O), 143.4 (C<sub>q</sub>-SO), 140.7 (aromatic C<sub>q</sub>-N), 131.6 (CH=CH-C=O), 129.8 (CH=CH-C=O), 129.3 (4 × aromatic CH), 129.2 (*p*-aromatic CH), 128.8 (*p*-aromatic CH), 124.4 (4 × aromatic CH), 62.3 (CH<sub>2</sub>-SO), 56.9 (CH<sub>2</sub>-N), 44.3 (C<sub>q</sub> ring), 24.3 (CH<sub>3</sub>-C<sub>q</sub>).

#### Cyclisation of sulfoxide amide 159



In a flame-dried flask and under a nitrogen atmosphere, dienone **159** (600 mg, 1.57 mmol) dissolved in THF (10 ml) was added slowly to a cooled to a suspension of sodium hydride (252 mg of 60 % dispersion in oil, 6.3 mmol, 4 equiv.) in dry THF (30 ml). The reaction mixture was stirred at room temperature for 19 hours then quenched with saturated NH<sub>4</sub>Cl solution (30 ml). The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 ml) and dried over Na<sub>2</sub>SO<sub>4</sub>. The combined extracts were concentrated *in vacuo* to afford 631 mg of a crude mixture of compounds **160**, **161**, and **162** as a fluffy yellow solid which was purified by flash chromatography (eluting with ethyl acetate-hexane 5:5) to afford the products in order as follows:

**(4*RS*,4*aSR*,8*aRS*)-4-Benzenesulfonyl-8*a*-methyl-2-phenyl-1,4*a*,5,8*a*-tetrahydro-2*H*,4*H*-isoquinoline-3,6-dione (**160**):** Pale yellow fluffy crystalline solid (56 mg, 21 %), m.p. 90 – 92 °C;  $\nu_{\text{max}}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3046, 2976, 1670, 1594, 1544, 1489, 1443, 1423, 1302, 1142, 1072, 733, 690;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.81 - 7.75 (2 H, m, 2 × aromatic CH), 7.58 - 7.53 (1 H, m, *p*-aromatic CH), 7.47 - 7.42 (2 H, m, 2 × aromatic CH), 7.35 - 7.29 (2 H, m, 2 × aromatic CH), 7.24 - 7.18 (1 H, m, *p*-aromatic CH), 7.14 - 7.04 (2 H, m, 2 × aromatic CH), 6.63 (1 H, dd, *J* 10.2, 2.0, CH=CH-C=O), 6.08 (1 H, d, *J* 10.2, CH=CH-C=O), 4.09 (1 H, d, *J* 12.7, one of CH<sub>2</sub>-N), 3.80 (1 H, d, *J* 5.8, CH-SO<sub>2</sub>), 3.40 (1 H, d, *J* 12.7, one of CH<sub>2</sub>-N), 3.37 (1 H, app. tt, 5.3, 2.3, ring junction CH), 2.97 (1 H, dd, *J* 17.6, 5.0, one of CH<sub>2</sub>-C=O), 2.69 (1 H, dd, *J* 17.6, 1.9, one of CH<sub>2</sub>-C=O), 1.35 (3 H, s, CH<sub>3</sub>-C<sub>q</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 195.6 (C=O), 164.8 (N-C=O), 153.2 (CH=CH-C=O), 142.1 (C<sub>q</sub>-SO<sub>2</sub>), 137.5 (C<sub>q</sub>-N), 134.3 (CH=CH-C=O), 131.7 (*p*-aromatic CH), 129.5 (2 × aromatic CH), 129.2 (2 × aromatic CH), 129.0 (2 × aromatic CH), 127.5 (*p*-aromatic CH), 125.3 (2 × aromatic CH), 71.2 (CH<sub>2</sub>-SO<sub>2</sub>), 59.8 (CH<sub>2</sub>-N), 40.8 (CH<sub>2</sub>-C=O), 39.3 (ring junction CH), 38.1 (C<sub>q</sub> ring), 22.7 (CH<sub>3</sub>).

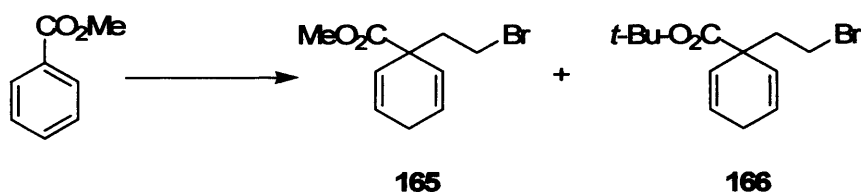
**Inseparable mixture of (S<sub>SR</sub>,4*SR*,4*aRS*,8*aSR*)-4-Benzenesulfinyl-8*a*-methyl-2-phenyl-1,4*a*,5,8*a*-tetrahydro-2*H*,4*H*-isoquinoline-3,6-dione (**161**) and (S<sub>SR</sub>,4*RS*,4*aSR*,8*aRS*)-4-Benzenesulfinyl-8*a*-methyl-2-phenyl-1,4*a*,5,8*a*-tetrahydro-2*H*,4*H*-isoquinoline-3,6-dione (**162**) (2:1):** Pale yellow solid (101 mg, 40 %);  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.65 - 7.15 (18 H, m, aromatic CH of both isomers), 6.85 (2 H, d, *J* 7.2, 2 × aromatic CH of minor isomer), 6.63 (1 H, dd, *J* 10.3, 1.8,

CH=CH-C=O of major isomer), 6.48 (1 H, dd,  $J$  10.2, 1.9, CH=CH-C=O of minor isomer), 6.05 (1 H, d,  $J$  10.2, CH=CH-C=O of minor isomer), 6.01 (1 H, d,  $J$  10.3, CH=CH-C=O of major isomer), 4.17 (1 H, d,  $J$  6.1, CH-SO of minor isomer), 4.01 (1 H, d,  $J$  12.6, one of CH<sub>2</sub>-N of major isomer), 3.34 (1 H, d,  $J$  12.6, one of CH<sub>2</sub>-N of major isomer), 3.29 (1 H, d,  $J$  5.3, CH-SO of major isomer), 2.97 - 2.92 (1 H, m, ring junction CH of major isomer), 2.91 (1 H, d,  $J$  12.6, one of CH<sub>2</sub>-NPh of minor isomer), 2.87 (1 H, dd,  $J$  17.4, 4.7, one of CH<sub>2</sub>-C=O of minor isomer), 2.85 - 2.80 (1 H, m, ring junction CH of minor isomer), 2.58 (1 H, app. broad d, 16.6, one of CH<sub>2</sub>-C=O of minor isomer), 2.37 (1 H, dd, 17.4, 5.1, one of CH<sub>2</sub>-C=O of major isomer), 2.29 (1 H, d,  $J$  12.6, one of CH<sub>2</sub>-NPh of minor isomer), 1.28 (3 H, s, CH<sub>3</sub> of major), 1.11 (3 H, s, CH<sub>3</sub> of minor isomer), 1.00 (1 H, dd,  $J$  17.4, 2.6, one of CH<sub>2</sub>-C=O of major isomer).

**8a-Methyl-2-phenyl-1,8a-dihydro-2H,4H-isoquinoline-3,6-dione (163):** Yellow oil (6 mg, 3.6 %) isolated from the second purification of the inseparable mixture of the major and the minor isomers;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>), 7.37 (2 H, app. t,  $J$  7.7, *m*-aromatic CH), 7.26 (1 H, app. t,  $J$  7.4, *p*-aromatic CH), 7.17 (2 H, app. d,  $J$  7.4, *o*-aromatic CH), 6.71 (1 H, d,  $J$  10.0, CH=CH-C=O), 6.32 (1 H, dd,  $J$  10.0, 1.6, CH=CH-C=O), 6.17 (1 H, broad s., O=C-CH=C<sub>q</sub>), 3.66 (1 H, dd,  $J$  20.2, 2.3, one of CH<sub>2</sub>-C=O), 3.55 (1 H, d,  $J$  11.9, one of CH<sub>2</sub>-N), 3.47 (1 H, d,  $J$  11.9, one of CH<sub>2</sub>-N), 3.43 (1 H, d,  $J$  20.2, one of CH<sub>2</sub>-C=O), 1.58 (3 H, s, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 185.1 (C=O), 166.0 (N-C=O), 157.2 (ring C<sub>q</sub>=CH), 153.2 (CH=CH-C=O), 141.9 (aromatic C<sub>q</sub>-N), 130.3 (*p*-aromatic CH), 129.7 (2 × *o*-aromatic CH), 127.7 (CH=CH-C=O), 126.2 (2 × *m*-aromatic CH), 125.5 (CH=CH-C=O), 65.9 (CH<sub>2</sub>-N), 58.4 (CH<sub>2</sub>-C=O), 38.7 (ring C<sub>q</sub>), 15.3 (CH<sub>3</sub>);  $m/z$  (APCI) 254.3 (MH<sup>+</sup>, 100 %), 240 (54).

### 6.3. Experimental Data for Chapter 3

#### Birch reduction/alkylation of methyl benzoate with 1,2-dibromoethane



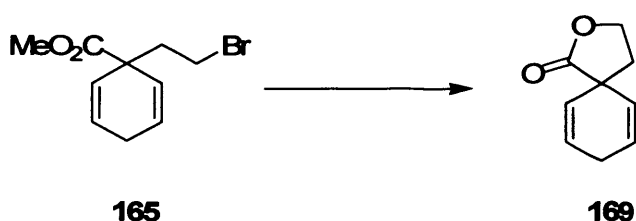
Ammonia (300 cm<sup>3</sup>) was condensed into a cooled solution (-78 °C) of methyl benzoate (5 g, 4.57 ml, 37 mmol) in THF (93 ml) containing *t*-butyl alcohol (3.4 g, 37 mmol, 1 equiv.) through a dry ice-acetone condenser. Potassium metal (5.1 g, 0.13 mmol) was added portion-wise until a blue colour persisted for 10 min. 1,2-Dibromoethane (15.9 ml, 185 mmol, 5 equiv.) was added slowly over a period of 5 min. The resulting mixture was stirred at that temperature for 15 min., then at -33 °C for 1.5 h. Solid ammonium chloride (7.3 g) was added carefully and the ammonia was allowed to evaporate overnight. Water was added to the residue and the solution was then extracted into diethyl ether (3 × 100 ml). The combined ethereal extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The remaining brown oil was purified by flash chromatography (eluting with ether–hexane 0.5:9.5) to afford compounds **166** and **165** in order as follows:

**6-(2'-Bromoethyl)-6-carbobutoxy-1,4-cyclohexadiene (166):** Pale brown oil (600 mg, 6 %);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 2966, 2925, 2725, 2664, 1773, 1721, 1368, 1261, 1159;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 5.93 (2 H, app. dt, *J* 10.4, 3.3, 2 × CH=CH-CH<sub>2</sub>), 5.70 (2 H, app. dt, *J* 10.4, 2.1, 2 × CH=CH-CH<sub>2</sub>), 3.32 – 3.17 (2 H, m, Br-CH<sub>2</sub>), 2.73 – 2.55 (2 H, m, ring CH<sub>2</sub>), 2.31 – 2.15 (2 H, m, Br-CH<sub>2</sub>-CH<sub>2</sub>), 1.46 (9 H, s, (CH<sub>3</sub>)<sub>3</sub>C);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 172.6 (C=O), 126.6 (2 × alkene CH), 126.1 (2 × alkene CH), 81.3 (O-C<sub>q</sub>), 48.9 (ring C<sub>q</sub>), 42.1 (Br-CH<sub>2</sub>), 28.2 (Br-CH<sub>2</sub>-CH<sub>2</sub>), 27.9 ((CH<sub>3</sub>)<sub>3</sub>C), 26.2 (ring CH<sub>2</sub>).

**6-(2-Bromoethyl)-6-Carbomethoxy-1,4-cyclohexadiene (165)**<sup>33, 34</sup>: Pale oil (1.2 g, 13.3 %) (Found: M+NH<sub>4</sub><sup>+</sup> 262.0438. C<sub>10</sub>H<sub>17</sub><sup>79</sup>BrNO<sub>2</sub> requires M, 262.0437);  $\nu_{\max}$

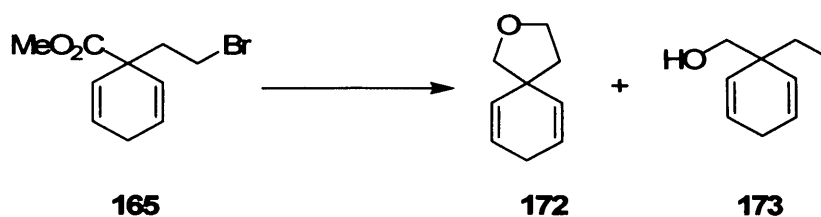
(neat)/cm<sup>-1</sup> 3011, 2875, 1731, 1433, 1238, 1210, 1072, 943, 798;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 5.95 (2 H, app. dt,  $J$  10.4, 3.3, 2  $\times$  CH=CH-CH<sub>2</sub>), 5.70 (2 H, app. dt,  $J$  10.4, 1.9, 2  $\times$  CH=CH-CH<sub>2</sub>), 3.70 (3 H, s, O-CH<sub>3</sub>), 3.26 – 3.20 (2 H, m, Br-CH<sub>2</sub>), 2.75 – 2.56 (2 H, m, ring CH<sub>2</sub>), 2.29 – 2.23 (2 H, m, Br-CH<sub>2</sub>-CH<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 174.0 (C=O), 127.0 (2  $\times$  alkene CH), 125.6 (2  $\times$  alkene CH), 52.5 (O-CH<sub>3</sub>), 48.2 (ring C<sub>q</sub>), 41.9 (Br-CH<sub>2</sub>), 27.9 (Br-CH<sub>2</sub>-CH<sub>2</sub>), 26.1 (ring CH<sub>2</sub>);  $m/z$  (APCI) 247 (M<sup>+</sup>, <sup>81</sup>Br, 26 %), 245 (29), 151 (19), 149 (9), 123 (23), 122 (68), 121 (100).

## 2-Oxa-spiro[4.5]deca-6,9-diene-1-one (169)



DMPU (1ml, 8 mmol, 2 equiv.) was added to a cooled (-78 °C) solution of methyl phenyl sulfoxide (572 mg, 4.1 mmol) in dry THF (20 ml). *n*-Butyllithium (2.5 M solution in hexane, 2 ml, 5 mmol, 1.23 equiv.) was added dropwise and the resulting mixture was stirred for 10 min. Bromocyclohexadiene **165** (1 g, 4.1 mmol) in THF (3 ml) was added and the reaction stirred at -78 °C for 1 h. then at room temperature for 20 h. Saturated ammonium chloride solution was added and the organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  20 ml). The combined extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (eluting with ether-hexane 3:7) afforded *the title lactone* (13 mg, 2 %) as a pale yellow oil;  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3060, 3032, 2915, 2362, 2362, 1769, 1266, 1162, 1026;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 5.96 (2 H, app. dt,  $J$  10.2, 3.4, 2  $\times$  CH=CH-CH<sub>2</sub>), 5.56 (2 H, app. dt,  $J$  10.2, 2.0, 2  $\times$  CH=CH-CH<sub>2</sub>), 4.32 (2 H, t,  $J$  7.0, O-CH<sub>2</sub>), 2.72 (1 H, app. dtt,  $J$  23.3, 3.8, 1.8, one of ring CH<sub>2</sub>), 2.64 (1 H, app. dtt,  $J$  23.3, 3.4, 2.0, one of ring CH<sub>2</sub>), 2.22 (2 H, t,  $J$  7.0, O-CH<sub>2</sub>-CH<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 178.1 (C=O), 127.6 (2  $\times$  alkene CH), 124.2 (2  $\times$  alkene CH), 65.2 (O-CH<sub>2</sub>), 45.3 (ring C<sub>q</sub>), 37.8 (CH<sub>2</sub>-C<sub>q</sub>), 26.0 (ring CH<sub>2</sub>);  $m/z$  (APCI) 151 (MH<sup>+</sup>, 11 %), 127 (36), 121 (100).

## Reduction of compound 165

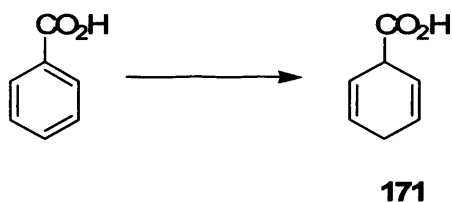


To a stirred suspension of  $\text{LiAlH}_4$  (2.47 g, 65 mmol) in dry THF (50 ml) under a nitrogen atmosphere at room temperature was added a solution of ester **165** (5.5 g, 22.4 mmol) in dry THF (10 ml). The mixture was stirred at room temperature for 1.5 hour. 15 % Aqueous NaOH solution (2.5 ml) was added carefully followed by addition of water (7.7 ml) and stirring was continued at room temperature for 48 h. Filtration and concentration under reduced pressure afforded a reddish yellow oil which was purified by flash chromatography (eluting with ether-hexane 1.5:8.5) to afford the following compounds in order as follows:

**2-Oxa-spiro[4.5]deca-6,9-diene (172):** Colourless oil (0.4 g, 13 %);  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3018, 2964, 2863, 1634, 1447, 1422, 1103, 1047, 966, 920;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.80 – 5.72 (2 H, m,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 5.70 – 5.63 (2 H, m,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 3.96 (2 H, t,  $J$  7.1,  $\text{O}-\text{CH}_2-\text{CH}_2$ ), 3.55 (2 H, s,  $\text{O}-\text{CH}_2-\text{Cq}$ ), 2.74 – 2.59 (2 H, m, ring  $\text{CH}_2$ ), 1.88 (2 H, t,  $J$  7.1,  $\text{CH}_2-\text{Cq}$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 130.4 ( $2 \times$  alkene CH), 123.7 ( $2 \times$  alkene CH), 79.7 ( $\text{O}-\text{CH}_2$ ), 67.8 ( $\text{O}-\text{CH}_2$ ), 43.8 ( $\text{C}_q$ ), 41.8 ( $\text{O}-\text{CH}_2-\text{CH}_2$ ), 26.3 ( $\text{CH}_2$ );  $m/z$  (APCI) 137 ( $\text{MH}^+$ , 29 %), 135 (11), 123 (19), 121 (100).

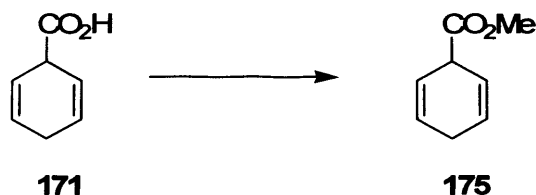
**1-Ethyl-cyclohexa-2,5-dienyl-methanol (173):** Pale yellow oil (222 mg, 7 %);  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3372, 3014, 2962, 2931, 2872, 1454, 1422, 1376, 1044, 956;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.97 – 5.90 (2 H, m,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 5.32 – 5.25 (2 H, m,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 3.27 (2 H, s,  $\text{CH}_2-\text{OH}$ ), 2.67 – 2.51 (2 H, m, ring  $\text{CH}_2$ ), 1.50 (1 H, broad s, OH), 1.21 (2 H, q,  $J$  7.5,  $\text{CH}_2-\text{CH}_3$ ), 0.73 (3 H, t,  $J$  7.5,  $\text{CH}_3-\text{CH}_2$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 129.6 ( $2 \times$  alkene CH), 127.9 ( $2 \times$  alkene CH), 70.5 ( $\text{O}-\text{CH}_2$ ), 44.0 ( $\text{C}_q$ ), 29.6 ( $\text{CH}_2-\text{CH}_3$ ), 26.3 (ring  $\text{CH}_2$ ), 8.7 ( $\text{CH}_3$ ).

### 2,5-Cyclohexadiene-1-carboxylic acid (**171**)<sup>48</sup>



Ammonia (600 cm<sup>3</sup>) was condensed into a cooled (-33 °C) solution of benzoic acid (10 g, 82 mmol) in anhydrous ethanol (100 ml) through a dry ice/acetone condenser. With careful stirring, sodium metal (6.2 g, 269.6 mmol, 3.3 equiv.) was added in small pieces. After addition of the sodium was completed, solid ammonium chloride (14.6 g, 0.27 mol) was added carefully and the mixture was stirred for a further one hour. The ammonia was allowed to evaporate overnight and the residue was dissolved in iced water. Aqueous 2 M HCl solution was added until pH 1 - 2 was reached. The organic material was then extracted into diethyl ether (3 × 200 ml). The combined ethereal extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford *the title acid* (9.6 g, 94 %) as an essentially-pure colourless oil;  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3040 (very broad), 1704, 1413, 1278, 1219, 1074, 941;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 11.60 (1 H, broad s, OH), 5.93 (2 H, app. dq,  $J$  10.4. 3.2, 2 × CH=CH-CH<sub>2</sub>), 5.84 (2 H, app. ddt,  $J$  10.4. 3.5, 1.8, 2 × CH=CH-CH<sub>2</sub>), 3.83 - 3.75 (1 H, m, CH-C=O), 2.80 - 2.62 (2 H, m, ring CH<sub>2</sub>);  $\delta_{\text{C}}$  (62.5 MHz; CDCl<sub>3</sub>) 178.9 (C=O), 126.9 (2 × alkene CH), 121.5 (2 × alkene CH), 41.5 (CH=CO), 25.8 (ring CH<sub>2</sub>).

### Cyclohexa-2,5-dienecarboxylic acid methyl ester (**175**)<sup>49</sup>



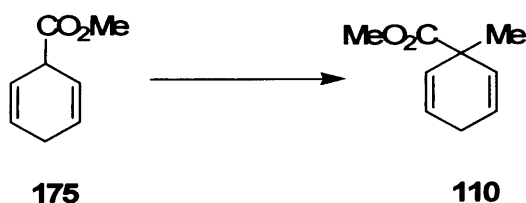
Conc. H<sub>2</sub>SO<sub>4</sub> (0.16 ml) was added to a solution of 2,5-cyclohexadiene-1-carboxylic acid (**171**) (7.9 g, 63.7 mmol) in absolute methanol (180 ml) at room temperature and under a nitrogen atmosphere. After stirring the reaction mixture for 24 h, most of the

solvent was evaporated under reduced pressure. The remaining solution was neutralised by addition of saturated  $\text{NaHCO}_3$  solution. The organic product was extracted into  $\text{CH}_2\text{Cl}_2$  ( $3 \times 50$  ml), dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to afford the *title ester* (7.4 g, 85 %) as an essentially-pure colourless oil which was used without further purification;  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3037, 2952, 2882, 1738, 1435, 1276, 1197, 1026, 941, 904;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.88 (2 H, app. dq,  $J$  10.4, 3.2,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 5.80 (2 H, app. ddt,  $J$  10.4, 3.3, 1.6,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 3.77 - 3.71 (1 H, m,  $\text{CH}-\text{C}=\text{O}$ ), 3.70 (3 H, s,  $\text{CH}_3$ ), 2.77 - 2.59 (2 H, m, ring  $\text{CH}_2$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 173.1 ( $\text{C}=\text{O}$ ), 126.5 ( $2 \times$  alkene CH), 122.1 ( $2 \times$  alkene CH), 52.2 ( $\text{O}-\text{CH}_3$ ), 41.2 ( $\text{CH}-\text{C}=\text{O}$ ), 25.8 (ring  $\text{CH}_2$ ).

### General Procedure for Deprotonation and Alkylation of compound 175

*n*-Butyllithium (2.5 M solution in hexane, 1.2 equiv.) was added to a cooled solution of *i*- $\text{Pr}_2\text{NH}$  (1.1 equiv.) in dry THF at  $-78^\circ\text{C}$ . After stirring the resulting mixture for 30 min, a solution of ester 175 (1 equiv.) in THF was added and the stirring was continued for another 30 min. The electrophile (1.1 equiv) was then added as a solution in THF and the reaction mixture was stirred for one hour at  $-78^\circ\text{C}$ , then at room temperature for 18 h. Saturated ammonium chloride solution was added and the product was extracted three times with  $\text{CH}_2\text{Cl}_2$ . The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to afford the crude product which was purified as described.

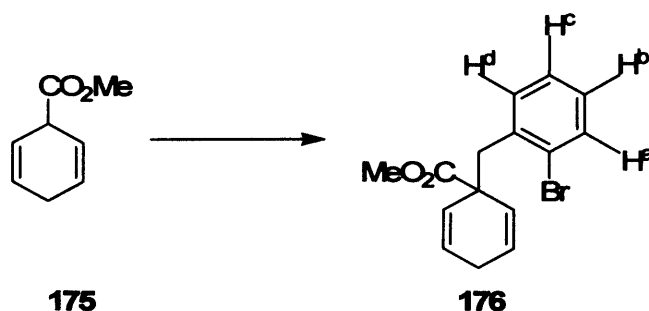
### 1-Methylcyclohexa-2,5-dienecarboxylic acid methyl ester(110)<sup>34</sup>



According to the general procedure above, ester 110 was obtained from substrate 175 (0.67 g, 4.9 mmol) in dry THF (5 ml) and iodomethane (0.34 ml, 5.4 mmol) in THF (3 ml) as an essentially-pure brown oil; yield 589 mg (79 %). The spectroscopic data are identical to those obtained by esterification of acid 108 (Page 154).

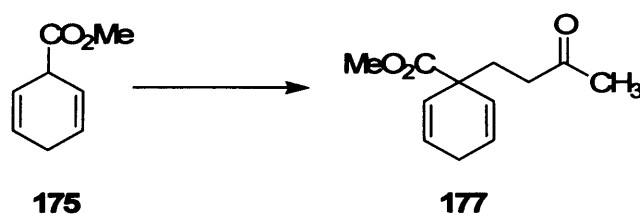


**1-(2-Bromobenzyl)-cyclohexa-2,5-dienecarboxylic acid methyl ester (176)**



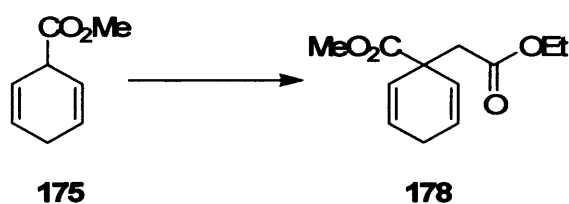
According to the general procedure above, compound **176** was obtained from substrate **175** (3.0 g, 21.7 mmol) in dry THF (10 ml) and 2-bromobenzyl bromide (6.0 g, 23.9 mmol) in THF (5 ml) as a dark yellow oil which was purified by flash chromatography (eluting with hexane-CH<sub>2</sub>Cl<sub>2</sub> 6:4) to afford the pure compound (4.7 g, 70 %) as a pale yellow oil (Found:  $M+NH_4^+$  324.0592. C<sub>15</sub>H<sub>19</sub>NO<sub>2</sub><sup>79</sup>Br requires  $M$ , 324.0594);  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3032, 2949, 2864, 1726, 1472, 1435, 1235, 1203, 1045, 1024, 736;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 7.43 (1 H, d,  $J$  8.2, aromatic H<sup>a</sup>), 7.11 – 7.05 (2 H, m, aromatic H<sup>b</sup> & H<sup>d</sup>), 7.00 – 6.94 (1 H, m, aromatic H<sup>c</sup>), 5.83 (2 H, app. dt,  $J$  10.4, 1.9, 2 × CH=CH-CH<sub>2</sub>), 5.73 (2 H, app. dt,  $J$  10.4, 3.3, 2 × CH=CH-CH<sub>2</sub>), 3.66 (3 H, s, O-CH<sub>3</sub>), 3.17 (2 H, s, Ar-CH<sub>2</sub>), 2.42 (1 H, app. dtt,  $J$  23.0, 3.3, 1.9, one of ring CH<sub>2</sub>), 2.17 (1 H, app. doubled quintet,  $J$  23.0, 2.6, one of ring CH<sub>2</sub>);  $\delta_C$  (100 MHz; CDCl<sub>3</sub>) 174.7 (O-C=O), 136.4 (C<sub>q</sub>-Br), 132.7 (aromatic CH), 132.1 (aromatic CH), 128.0 (aromatic CH), 126.6 (aromatic CH), 126.5 (2 × alkene CH), 126.3 (aromatic C<sub>q</sub>-CH<sub>2</sub>), 126.2 (2 × alkene CH), 52.3 (O-CH<sub>3</sub>), 49.3 (C<sub>q</sub>-C=O), 44.2 (Ar-CH<sub>2</sub>), 25.8 (ring CH<sub>2</sub>);  $m/z$  (APCI) 309 ( $M^+$  (<sup>81</sup>Br), 13 %), 307 ( $M^+$  (<sup>79</sup>Br), 12 %), 249 (32), 247 (39), 187 (36), 185 (59), 171 (17), 169 (23), 137 (100).

**1-(3-Oxo-butyl)-cyclohexa-2,5-dieneacboxylic acid methyl ester (177)**



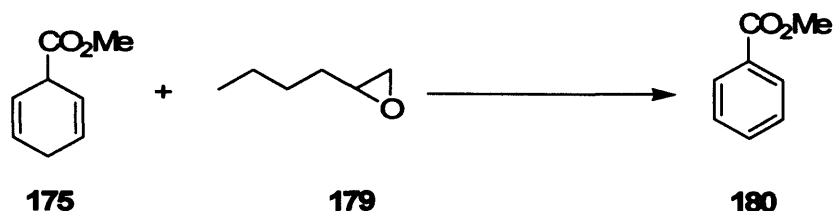
According to the general procedure above, compound **177** was obtained from ester **175** (0.5 g, 3.6 mmol) in dry THF (5 ml) and methyl vinyl ketone (280 mg, 0.33 ml, 4 mmol) in THF (3 ml) as a reddish yellow oil which was purified by flash chromatography (eluting with CH<sub>2</sub>Cl<sub>2</sub>) to afford the pure *title compound* (265 mg, 35 %) as a pale yellow oil;  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3032, 2952, 1728, 1434, 1365, 1235, 1084, 1021, 796;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 5.89 - 5.82 (2 H, m, 2 × CH=CH-CH<sub>2</sub>), 5.63 - 5.57 (2 H, m, 2 × CH=CH-CH<sub>2</sub>), 3.62 (3 H, s, O-CH<sub>3</sub>), 2.69 - 2.51 (2 H, m, ring CH<sub>2</sub>), 2.29 (2 H, t, *J* 7.8, CH<sub>2</sub>-C=O), 2.05 (3 H, s, CH<sub>3</sub>-C=O), 1.91 (2 H, app. t, *J* 7.8, CH<sub>2</sub>-Cq);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 208.4 (C=O), 174.9 (O-C=O), 126.6 (2 × alkene CH), 126.5 (2 × alkene CH), 52.3 (O-CH<sub>3</sub>), 47.1 (ring C<sub>q</sub>), 38.7 (CH<sub>2</sub>-CH<sub>2</sub>-C=O), 32.5 (CH<sub>2</sub>-CH<sub>2</sub>-C=O), 30.1 (CH<sub>3</sub>-C=O), 26.1 (ring CH<sub>2</sub>).

#### 1-Ethoxycarbonylmethyl-cyclohexa-2,5-dienecarboxylic acid methyl ester (**178**)



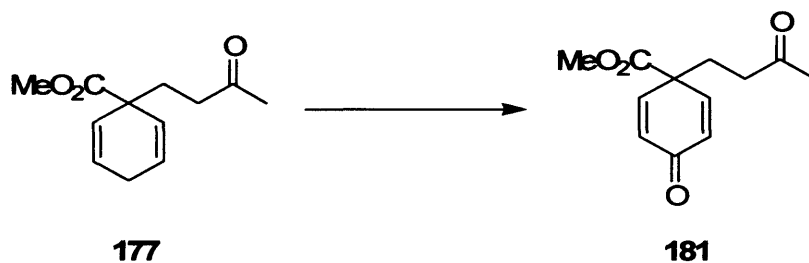
According to the general procedure above, compound **178** was obtained from ester **175** (1.0 g, 7.3 mmol) in dry THF (5 ml) and ethyl 2-bromoacetate (1.3 g, 0.88 ml, 8.0 mmol) in THF (3 ml) as an essentially-pure yellow oil (1.2 g, 73 %);  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 2982, 2952, 1732, 1435, 1370, 1338, 1236, 1176, 1028, 888;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 5.84 (2 H, app. dt, *J* 10.4, 3.3, 2 × CH=CH-CH<sub>2</sub>), 5.74 (2 H, app. dt, *J* 10.4, 1.8, 2 × CH=CH-CH<sub>2</sub>), 4.04 (2 H, q, *J* 7.2, O-CH<sub>2</sub>), 3.67 (3 H, s, O-CH<sub>3</sub>), 2.66 (2 H, s, CH<sub>2</sub>-C<sub>q</sub>), 2.68 - 2.52 (2 H, m, ring CH<sub>2</sub>), 1.17 (3 H, t, *J* 7.2, CH<sub>3</sub>-CH<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 174.1 (O-C=O), 170.4 (O-C=O), 126.3 (4 × alkene CH), 60.5 (O-CH<sub>2</sub>), 52.5 (O-CH<sub>3</sub>), 45.6 (ring C<sub>q</sub>), 44.6 (CH<sub>2</sub>-C<sub>q</sub>), 25.9 (ring CH<sub>2</sub>), 14.1 (CH<sub>3</sub>-CH<sub>2</sub>).

### Methyl benzoate (180)



According to the general procedure above, methyl benzoate **180** was obtained from ester **175** (376 mg, 2.73 mmol) in dry THF (2 ml) and 2-butyl-oxirane **179** (0.3 g, 3.0 mmol) in THF (2 ml) as an essentially-pure brown oil (237 mg, 64 %);  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  2952, 1723, 1436, 1316, 1281, 1113, 910;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.97 (2 H, dd,  $J$  8.3, 1.3,  $2 \times o$ -aromatic CH), 7.49 (1 H, app. tt,  $J$  7.8, 1.3,  $p$ -aromatic CH), 7.35 (2 H, app. t,  $J$  7.8,  $2 \times m$ -aromatic CH), 3.94 (3 H, s, O- $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 167.1 (O-C=O), 132.9 ( $p$ -aromatic CH), 130.1 (aromatic C), 129.6 ( $2 \times o$ -aromatic CH), 128.3 ( $2 \times m$ -aromatic CH), 52.1 (O- $\text{CH}_3$ ). The obtained data are in line with those from an authentic sample.

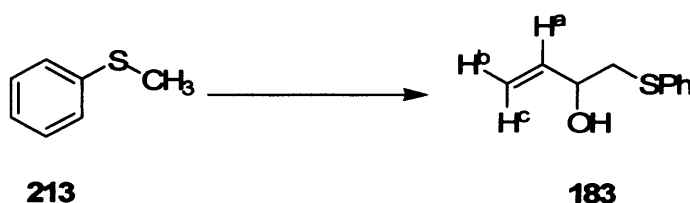
### 4-Oxo-1-(3-oxo-butyl)-cyclohexa-2,5-dienecarboxylic acid methyl ester (181)



Celite (2.8 g) was added to a cooled ( $0\text{ }^{\circ}\text{C}$ ) suspension of substrate **177** (477 mg, 2.29 mmol) in benzene (40 ml) in a flame-dried flask. 5 - 6 M  $t$ -BuOOH in decane (1.8 ml, 9.1 mmol, 4 equiv.) was added. This was followed by portion-wise addition of pyridinium dichromate (3.4 g, 9.1 mmol, 4 equiv.) over 10 min. The resulting mixture was stirred at room temperature for 18 hours. After dilution with ether and filtration through a pad of basic alumina type H, the combined solutions were concentrated *in vacuo* to afford a dark green viscous oil. Purification by column chromatography (eluting with ethyl acetate- $\text{CH}_2\text{Cl}_2$  1:9) afforded the *title dienone*

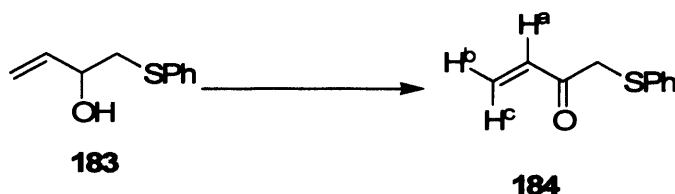
(275 mg, 54 %) as a pale yellow oil;  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  2956, 1732, 1667, 1629, 1434, 1402, 1367, 1236, 1174, 1083, 1022, 860;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 6.91 (2 H, d,  $J$  10.3,  $2 \times \text{CH}=\text{CH}-\text{C}=\text{O}$ ), 6.32 (2 H, d,  $J$  10.3,  $2 \times \text{CH}=\text{CH}-\text{C}=\text{O}$ ), 3.57 (3 H, s, O- $\text{CH}_3$ ), 2.25 (4 H, app. s,  $\text{C}_q-\text{CH}_2-\text{CH}_2$ ), 2.05 (3 H, s,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 206.5 (ketone  $\text{C}=\text{O}$ ), 184.9 (conjugated  $\text{C}=\text{O}$ ), 170.4 (O- $\text{C}=\text{O}$ ), 147.4 ( $2 \times \text{CH}=\text{CH}-\text{C}=\text{O}$ ), 130.7 ( $2 \times \text{CH}=\text{CH}-\text{C}=\text{O}$ ), 53.3 (O- $\text{CH}_3$ ), 51.5 (ring  $\text{C}_q$ ), 37.5 ( $\text{CH}_2-\text{C}=\text{O}$ ), 30.8 ( $\text{CH}_2-\text{C}_q$ ), 30.2 ( $\text{CH}_3$ ).

### 1-Phenylsulfanyl-but-3-en-2-ol (**183**)<sup>53</sup>



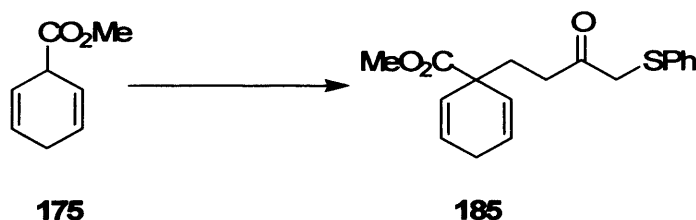
Thioanisole **213** (8.6 g, 8.1 ml, 69.2 mmol) was added to a solution of DABCO (8 g, 71.3 mmol, 1.03 equiv.) in dry THF (120 ml) under a nitrogen atmosphere. The resulting suspension was cooled to 0 °C then *n*-butyllithium (2.5 M solution in hexane, 38.4 ml, 96 mmol, 1.38 equiv.) was added dropwise. After removal of the cooling bath the resulting mixture was stirred at room temperature for one hour. The reaction was then cooled to -78 °C and acrolein (12.4 g, 14.8 ml, 221.2 mmol, 3.2 equiv) added over 30 min. The reaction mixture was allowed to warm up to room temperature and stirring was continued for 18 hours. Saturated ammonium chloride solution (50 ml) was added and the product was extracted into ether (3  $\times$  60 ml). The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to afford the *title compound* **183** (12.3 g, 99 %) as an essentially-pure brown oil;  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3382, 3076, 2916, 1582, 1479, 1438, 1087, 828;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.30 – 7.05 (5 H, m, aromatic CH), 5.76 (1 H, app. ddd,  $J$  17.1, 10.5, 5.9,  $\text{H}^a$ ), 5.20 (1 H, dd,  $J$  17.1, 0.9,  $\text{H}^c$ ), 5.06 (1 H, dd,  $J$  10.5, 0.9,  $\text{H}^b$ ), 4.11 (1 H, m,  $\text{CH}-\text{OH}$ ), 3.03 (1 H, dd,  $J$  13.6, 5.3, one of S- $\text{CH}_2$ ), 2.84 (1 H, dd,  $J$  13.6, 8.2, one of S- $\text{CH}_2$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 138.4 (alkene CH), 135.1 ( $\text{C}_q-\text{S}$ ), 130.2 ( $2 \times o$ -aromatic CH), 129.1 ( $2 \times m$ -aromatic CH), 126.7 (*p*-aromatic CH), 116.3 (alkene  $\text{CH}_2$ ), 70.5 (O-CH), 41.7 (S- $\text{CH}_2$ ).

### 1-Phenylsulfanyl-but-3-en-2-one (184)<sup>52</sup>



IBX (10.41 g, 37.18 mmol, 2.5 equiv.) in DMSO (50 ml) was stirred at room temperature until homogenous and clear solution was obtained (30 min.). A solution of vinyl alcohol **183** (2.7 g, 14.87 mmol) in DMSO (13 ml) was added and the mixture was stirred at this temperature for 6 h giving a yellow suspension. Water (133 ml) was added and the mixture was stirred for 10 min then cooled to 0 °C and stirred at this temperature for 45 min. The mixture was then partitioned between water (150 ml) and ether (150 ml) and the organic material was extracted into the ethereal layer. Then this extract was washed several times with water and the combined ethereal extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford vinyl ketone **184** (1.56 g, 59 %) as an essentially-pure reddish yellow oil;  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3060, 2930, 1704, 1582, 1479, 1437, 1400, 1249, 1042, 742;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.32 – 7.27 (2 H, m, aromatic CH), 7.25 – 7.18 (2 H, m, aromatic CH), 7.16 (1 H, app. tt, *J* 7.2, 1.3, aromatic CH), 6.53 (1 H, dd, *J* 17.5, 10.6 H<sup>a</sup>), 6.23 (1 H, dd, *J* 17.5, 1.0, H<sup>c</sup>), 5.77 (1 H, dd, *J* 10.6, 1.0, H<sup>b</sup>), 3.75 (2 H, s, S-CH<sub>2</sub>).

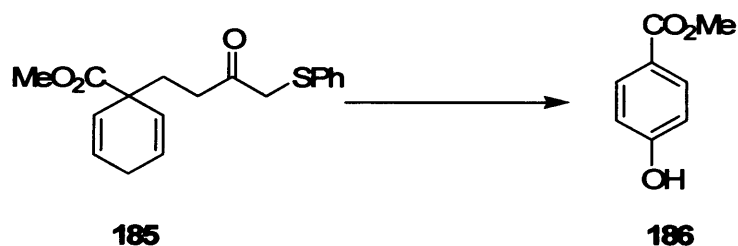
### 1-(3-Oxo-4-phenylsulfanyl-butyl)-cyclohexa-2,5-dienecarboxylic acid methyl ester (185)



*n*-Butyllithium (2.5 M solution in hexane, 3.5 ml, 8.7 mmol, 1.0 equiv.) was added to a cooled (−78 °C) solution of *i*-Pr<sub>2</sub>NH (0.8 g, 1.1 ml, 7.9 mmol, 1.0 equiv.) in dry THF (10 ml). After stirring the resulting mixture for half an hour, a solution of ester

**175** (1.0 g, 7.2 mmol, 1.0 equiv.) in THF (3 ml) was added and the stirring was continued for another half an hour. Vinyl ketone **184** (1.4 g, 7.9 mmol, 1.1 equiv) in THF (3 ml) was added and the reaction mixture was stirred for three hours. Saturated ammonium chloride solution (15 ml) was added and the product was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 ml). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give a yellow oil which was purified by flash chromatography (eluting with hexane-ethyl acetate in gradient mode 9:1 to 6:4) to afford the pure *title compound* (641 mg, 29 %) as a pale yellow oil (Found: M+NH<sub>4</sub><sup>+</sup> 334.1475. C<sub>18</sub>H<sub>24</sub>NSO<sub>3</sub> requires M, 334.1471);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3032, 2950, 1728, 1583, 1481, 1438, 1235, 1203, 1050, 740, 691;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.27 – 7.19 (5 H, m, aromatic CH), 5.82 (2 H, app. dt, *J* 10.5, 3.5, 2 × CH=CH-CH<sub>2</sub>), 5.55 (2 H, app. dt, *J* 10.5, 2.0, 2 × CH=CH-CH<sub>2</sub>), 3.61 (3 H, s, O-CH<sub>3</sub>), 3.57 (2 H, s, S-CH<sub>2</sub>), 2.64 – 2.46 (2 H, m, ring CH<sub>2</sub>), 2.46 – 2.41 (2 H, m, CH<sub>2</sub>-CH<sub>2</sub>-C=O), 1.92 – 1.86 (2 H, m, CH<sub>2</sub>-CH<sub>2</sub>-C=O);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 205.2 (C=O), 174.8 (O-C=O), 134.8 (C<sub>q</sub>-S), 129.7 (2 × *o*-aromatic CH), 129.2 (2 × *m*-aromatic CH), 126.9 (*p*-aromatic CH), 126.7 (2 × alkene CH), 126.3 (2 × alkene CH), 52.4 (CH<sub>3</sub>), 47.2 (ring C<sub>q</sub>), 44.1 (S-CH<sub>2</sub>), 35.9 (CH<sub>2</sub>-C=O), 32.5 (CH<sub>2</sub>-CH<sub>2</sub>-C=O), 26.1 (ring CH<sub>2</sub>); *m/z* (APCI) 317 (MH<sup>+</sup>, 100 %), 257 (10 %), 156 (100), 153 (11).

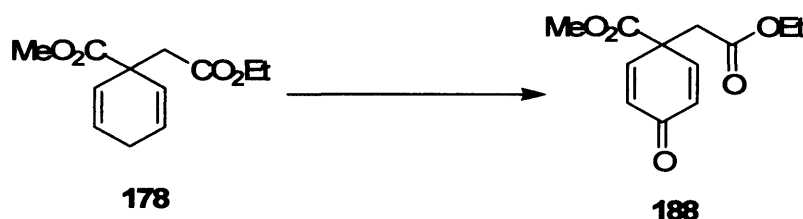
#### Methyl 4-hydroxybenzoate (**186**)



Celite (1.0 g) was added to a cooled (0 °C) suspension of the substrate **185** (101 mg, 0.32 mmol) in dry benzene (15 ml) in a flame dried flask. 5 - 6 M *t*-BuOOH in decane (0.26 ml, 1.3 mmol, 4.1 equiv.) was added. This was followed by portion-wise addition of pyridinium dichromate (480 mg, 1.3 mmol, 4.1 equiv.) over 10 min. The resulting mixture was stirred at room temperature for 24 hours. After dilution with ethyl acetate and filtration through a plug of celite, the combined solutions were concentrated *in vacuo* to afford a brown oil. Purification by column

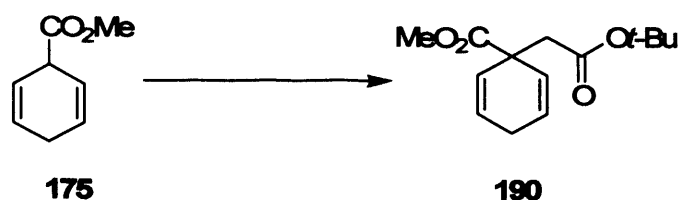
chromatography (eluting with ethyl acetate-hexane 1:9) afforded the *title compound* (46 mg, 96 %) as a yellow oil;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.88 (2H, d,  $J$  8.6,  $2 \times \text{CH}$ ), 6.81 (2H, d,  $J$  8.6,  $2 \times \text{CH}$ ), 6.48 (1H, broad s, OH), 3.82 (3H, s,  $\text{CH}_3$ ). These data are consistent with those reported in the Aldrich Library of  $^{13}\text{C}$  and  $^1\text{H}$  FT-NMR Spectra.

**1-Ethoxycarbonylmethyl-4-oxo-cyclohexa-2,5-dienecarboxylic acid methyl ester (188)**



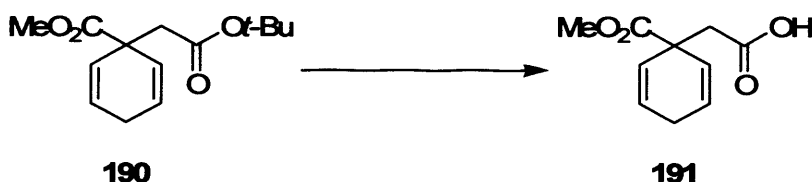
Celite (2.5 g) was added to a cooled (0 °C) suspension of substrate **178** (500 mg, 2.23 mmol) in benzene (40 ml) in a flame-dried flask. 5 - 6 M *t*-BuOOH in decane (1.8 ml, 8.9 mmol, 4 equiv.) was added. This was followed by portion-wise addition of pyridinium dichromate (3.3 g, 8.9 mmol, 4 equiv.) over 10 min. The resulting mixture was stirred at room temperature for 24 hours. After dilution with  $\text{CH}_2\text{Cl}_2$  and filtration through a plug of celite, the combined solutions were concentrated *in vacuo* to afford the *title compound* (436 mg, 82 %) as an slightly impure (contaminated with benzene) yellow oil;  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  2957, 2929, 1733, 1673, 1632, 1435, 1372, 1175, 1070, 1026, 860;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 6.99 (2 H, d,  $J$  10.1,  $2 \times \text{CH}=\text{CH}-\text{C}=\text{O}$ ), 6.29 (2 H, d,  $J$  10.1,  $2 \times \text{CH}=\text{CH}-\text{C}=\text{O}$ ), 4.07 (2 H, q,  $J$  7.1, O- $\text{CH}_2$ ), 3.64 (3 H, s, O- $\text{CH}_3$ ), 2.78 (2 H, s,  $\text{CH}_2-\text{C}=\text{O}$ ), 1.15 (3 H, t,  $J$  7.1, O- $\text{CH}_2-\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 184.7 (ketone  $\text{C}=\text{O}$ ), 170.1 (O- $\text{C}=\text{O}$ ), 169.3 (O- $\text{C}=\text{O}$ ), 146.4 ( $2 \times \text{CH}=\text{CH}-\text{C}=\text{O}$ ), 130.5 ( $2 \times \text{CH}=\text{CH}-\text{C}=\text{O}$ ), 61.4 (O- $\text{CH}_2$ ), 53.5 (O- $\text{CH}_3$ ), 49.6 (ring  $\text{C}_q$ ), 41.6 ( $\text{CH}_2-\text{C}_q$ ), 14.1 ( $\text{CH}_3-\text{CH}_2$ ).

**Methyl 1-((*tert*-butoxycarbonyl)methyl)cyclohexa-2,5-dienecarboxylate (190)**



According to the general procedure on page 192, compound **190** was obtained from ester **175** (4.0 g, 28.9 mmol) in dry THF (7 ml) and *t*-butyl 2-bromoacetate (6.2 g, 4.7 ml, 31.9 mmol) in THF (5 ml) as an essentially-pure pale yellow oil (6.2 g, 85 %);  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 2980, 1729, 1454, 1436, 1394, 1369, 1280, 1253, 1156, 847, 716;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 5.82 (2 H, app. dt, *J* 10.2, 3.1, 2 × CH=CH-CH<sub>2</sub>), 5.73 (2 H, app. dt, *J* 10.2, 1.5, 2 × CH=CH-CH<sub>2</sub>), 3.64 (3 H, s, O-CH<sub>3</sub>), 2.69 – 2.52 (2 H, m, ring CH<sub>2</sub>), 2.57 (2 H, s, C<sub>q</sub>-CH<sub>2</sub>), 1.37 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 174.1 (O-C=O), 169.6 (O-C=O), 126.5 (2 × alkene CH), 126.1 (2 × alkene CH), 80.9 (O-C(CH<sub>3</sub>)<sub>3</sub>), 52.4 (O-CH<sub>3</sub>), 45.9 (CH<sub>2</sub>-C<sub>q</sub>), 45.8 (ring C<sub>q</sub>), 28.0 (C(CH<sub>3</sub>)<sub>3</sub>), 26.0 (ring CH<sub>2</sub>).

**2-(1-(methoxycarbonyl)cyclohexa-2,5-dienyl)acetic acid (191)**

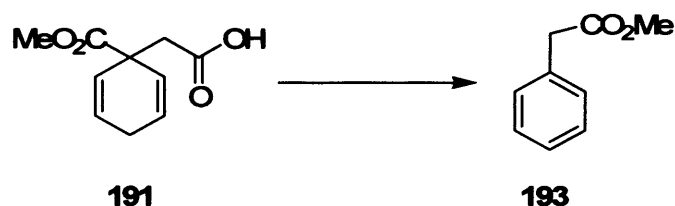


Trifluoroacetic acid (6.8 ml, 89 mmol, 22.5 equiv.) was added to a solution of the diester **190** (1.0 g, 3.96 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 ml). The resulting mixture was stirred at room temperature for 48 hours, then diluted with water and aqueous 2 M HCl solution. The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml) and the combined extracts dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the residue washed with petroleum ether to afford the *title compound* (752 mg, 96 %) as a pale brown crystalline solid, m.p. 67 – 69 °C (Found: MH<sup>+</sup> 197.0808. C<sub>10</sub>H<sub>13</sub>O<sub>4</sub> requires M, 197.0808);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3498 (broad), 3044, 2946, 1724, 1434, 1388, 1203, 1089, 1052, 942, 888, 715;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>)



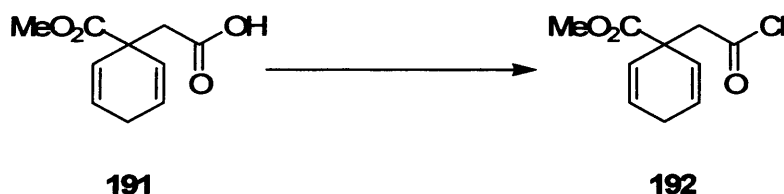
5.84 (2 H, app. dt,  $J$  10.3, 3.3,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 5.71 (2 H, app. dt,  $J$  10.3, 1.9,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 3.63 (3 H, s, O-CH<sub>3</sub>), 2.71 (2 H, s, CH<sub>2</sub>-C=O), 2.68 – 2.52 (2 H, m, ring CH<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 176.2 (HO-C=O), 174.1 (O-C=O), 126.8 ( $2 \times$  alkene CH), 125.9 ( $2 \times$  alkene CH), 52.7 (O-CH<sub>3</sub>), 45.5 (ring C<sub>q</sub>), 44.1 ( $\text{CH}_2-\text{C}=\text{O}$ ), 26.0 (ring CH<sub>2</sub>);  $m/z$  (APCI) 317 (MH<sup>+</sup>, 72 %), 179 (10), 165 (19), 151 (26), 137 (100).

### Methyl 2-phenylacetate (193)



Thionyl chloride (5 ml, 68.6 mmol, 78 equiv.) was added to acid **191** (172 mg, 0.88 mmol), and the resulting mixture was heated under reflux for 18 hours. Excess thionyl chloride was removed *in vacuo* to leave the *title compound* (119 mg, 90 %) as a pale brown oil;  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3031, 2953, 1738, 1496, 1435, 1257, 1160, 1014, 723;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.19 – 7.07 (5 H, m, aromatic CH), 3.52 (3 H, s, CH<sub>3</sub>), 3.46 (2 H, s, CH<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 172.1 (O-C=O), 134.0 (aromatic C<sub>q</sub>), 129.3 ( $2 \times$  aromatic CH), 128.6 ( $2 \times$  aromatic CH), 126.9 (*p*-aromatic CH), 52.1 (CH<sub>3</sub>), 41.2 (CH<sub>2</sub>).

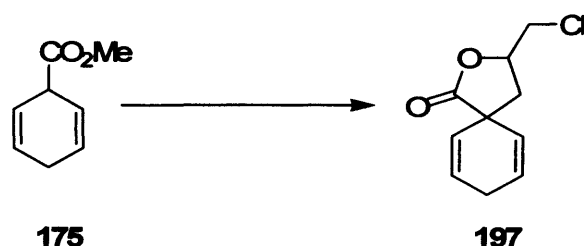
### Methyl 1-((chlorocarbonyl)methyl)cyclohexa-2,5-dienecarboxylate (192)



Thionyl chloride (1.6 g, 5 ml, 13.34 mmol, 1.6 equiv.) was added to a solution of acid **191** (1.65 g, 1.0 ml, 8.4 mmol) in toluene (20 ml). DMF (0.03 ml) was added and the resulting mixture was heated at 40 °C for two hours then at 60 °C for one

hour. The excess thionyl chloride and toluene were removed *in vacuo* at 60 °C to afford the *title acid chloride 192* in quantitative yield as a brown oil which was used without further purification;  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3025, 2946, 2875, 1800, 1730, 1434, 1391, 1248, 1125, 1054, 968, 704;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 5.91 (2 H, app. dt, *J* 10.4, 3.4, 2 × CH=CH-CH<sub>2</sub>), 5.68 (2 H, app. dt, *J* 10.4, 2.0, 2 × CH=CH-CH<sub>2</sub>), 3.66 (3 H, s, O-CH<sub>3</sub>), 3.26 (2 H, s, CH<sub>2</sub>-C=O), 2.73 – 2.56 (2 H, m, ring CH<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 173.0 (Cl-C=O), 171.0 (O-C=O), 127.6 (2 × alkene CH), 124.9 (2 × alkene CH), 56.1 (CH<sub>2</sub>-C=O), 52.9 (O-CH<sub>3</sub>), 46.5 (ring C<sub>q</sub>), 26.0 (ring CH<sub>2</sub>).

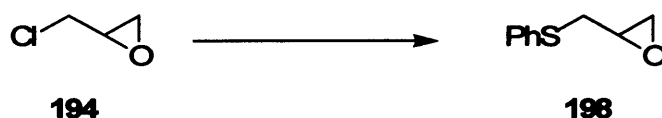
### 3-Chloromethyl-2-oxa-spiro[4.5]deca-6,9-dien-1-one (197)



*n*-Butyllithium (2.5 M solution in hexane, 2.9 ml, 7.2 mmol, 1.0 equiv.) was added to a cooled (−78 °C) solution of *i*-Pr<sub>2</sub>NH (1.0 ml, 7.2 mmol, 1.0 equiv.) in dry THF (10 ml). After stirring the resulting mixture for half an hour, a solution of ester **175** (1.0 g, 7.2 mmol) in THF (3 ml) was added and stirring was continued for a further half an hour. Epichlorohydrin **194** (0.73 g, 0.62 ml, 7.9 mmol, 1.1 equiv) was added and the reaction mixture was stirred for one hour at −78 °C followed by 18 hours at room temperature. Saturated ammonium chloride solution (20 ml) was added and the product was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford a yellow solid which was purified by flash column chromatography (eluting with hexane-ethyl acetate 8:2) to afford the *title compound* (691 mg, 48 %) as a colourless waxy solid m.p. 55 – 57 °C (Found: MH<sup>+</sup> 199.0519 C<sub>10</sub>H<sub>12</sub>O<sub>2</sub><sup>35</sup>Cl requires M, 199.0520);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3031, 2875, 2825, 1767, 1634, 1418, 1333, 1167, 1042, 882;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 6.00 (1 H, app. ddt, *J* 10.0, 3.6, 1.3, one of CH=CH-CH<sub>2</sub>), 5.93 (1 H, app. ddt, *J* 10.0, 3.4, 1.3, one of CH=CH-CH<sub>2</sub>), 5.63 (1 H, app. dq, *J* 10.0, 2.0, one of CH=CH-CH<sub>2</sub>), 5.49 (1 H, app. dq, *J* 10.0, 2.0, one of CH=CH-CH<sub>2</sub>), 4.73 (1 H, app. ddt, *J* 9.5, 6.2, 5.0, O-CH), 3.68 (2 H, app. d, *J* 5.0, CH<sub>2</sub>Cl), 2.81 – 2.71 (1 H, m, one

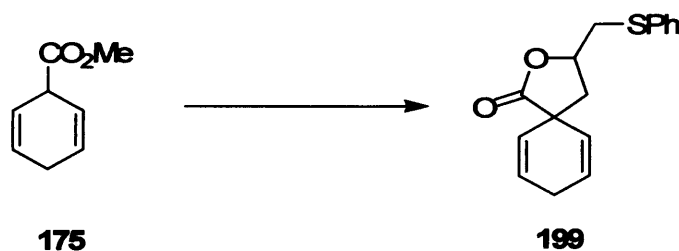
of ring CH<sub>2</sub>), 2.69 – 2.59 (1 H, m, one of ring CH<sub>2</sub>), 2.32 (1 H, dd, *J* 13.2, 6.3, one of CH<sub>2</sub>C<sub>q</sub>), 2.11 (1 H, dd, *J* 13.2, 9.5, one of CH<sub>2</sub>-C<sub>q</sub>);  $\delta_c$  (100 MHz; CDCl<sub>3</sub>) 176.7 (O-C=O), 128.1 (alkene CH), 127.5 (alkene CH), 125.2 (alkene CH), 123.3 (alkene CH), 75.3 (O-CH), 46.8 (ring C<sub>q</sub>), 45.5 (CH<sub>2</sub>-Cl), 41.1 (CH<sub>2</sub>-C<sub>q</sub>), 25.9 (ring CH<sub>2</sub>); *m/z* (APCI) 201 (MH<sup>+</sup>, <sup>37</sup>Cl, 35 %), 199 (100), 157 (10), 155 (36), 153 (8), 123 (8).

### 2-Phenylsulfanylmethyl-oxirane (199)<sup>56</sup>



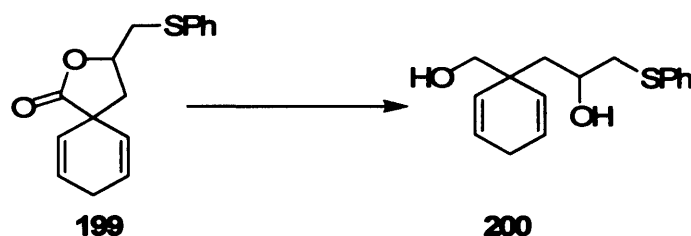
Sodium hydroxide pellets (14.1 g, 352 mmol, 2.9 equiv.) were added to a solution of epichlorohydrin **194** (18.4 ml, 235 mmol, 1.9 equiv.) in dioxane (50 ml). Benzenethiol (12.4 ml, 120.8 mmol) in dioxane (20 ml) was added dropwise and the resulting mixture was stirred at room temperature for 18 hours. Filtration and concentration *in vacuo* afforded the *title compound* (16.5 g, 82 %) as an essentially-pure colourless oil;  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3056, 2993, 2919, 1584, 1480, 1438, 1264, 1087, 1025, 950, 923, 828;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 7.45 (2 H, d, *J* 7.4, 2 × *o*-aromatic CH), 7.32 (2 H, app. t, *J* 7.6, 2 × *m*-aromatic CH), 7.24 (1 H, app. t, *J* 7.3, *p*-aromatic CH), 3.22 - 3.14 (2 H, m, O-CH and one of S-CH<sub>2</sub>), 2.96 (1 H, dd, *J* 15.3, 7.2, one of S-CH<sub>2</sub>), 2.77 (1 H, app. t, *J* 4.2, one of O-CH<sub>2</sub>), 2.52 (1 H, app. dd, *J* 4.9, 2.3 one of O-CH<sub>2</sub>);  $\delta_c$  (62.5 MHz; CDCl<sub>3</sub>) 135.3 (C<sub>q</sub>-S), 130.4 (2 × *o*-aromatic CH), 129.1 (2 × *m*-aromatic CH), 126.8 (*p*-aromatic CH), 51.1 (O-CH<sub>2</sub>), 47.4 (O-CH), 36.7 (S-CH<sub>2</sub>).

### 3-Phenylsulfanylmethyl-2-oxa-spiro[4.5]deca-6,9-dien-1-one (199)



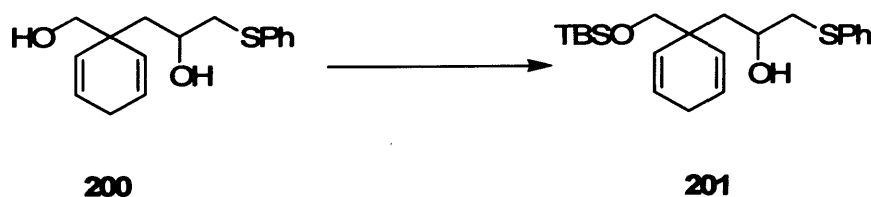
*n*-Butyllithium (2.5 M solution in hexane, 2.96 ml, 7.4 mmol, 1.0 equiv.) was added to a cooled (0 °C) solution of *i*-Pr<sub>2</sub>NH (0.75 g, 1.0 ml, 7.4 mmol, 1.0 equiv.) in dry THF (10 ml). After stirring the resulting mixture for half an hour, the reaction was cooled to –78 °C and a solution of ester **175** (1.02 g, 7.4 mmol) in THF (3 ml) was added. Stirring was continued for half an hour and epoxide **198** (1.34 g, 8.1 mmol, 1.1 equiv) was added. The reaction mixture was stirred for one hour at –78 °C, then at room temperature for 18 hours. Saturated ammonium chloride solution (20 ml) was added and the product extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give a yellow solid which was purified by flash column chromatography (eluting with hexane-ethyl acetate 9:1) to afford the *title compound* (1.4 g, 70 %) as a pale yellow waxy solid m.p. 60 – 62 °C (Found: MH<sup>+</sup> 273.0943. C<sub>16</sub>H<sub>17</sub>SO<sub>2</sub> requires M, 273.0944);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>–1</sup> 3026, 2925, 2875, 2805, 1771, 1582, 1481, 1439, 1171, 985, 738;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.37 – 7.32 (2 H, m, 2 × *o*-aromatic CH), 7.27 – 7.22 (2 H, m, 2 × *m*-aromatic CH), 7.21 – 7.15 (1 H, m, *p*-aromatic CH), 5.98 (1 H, app. ddt, *J* 10.0, 3.4, 1.4, one of CH=CH-CH<sub>2</sub>), 5.89 (1 H, app. ddt, *J* 10.0, 3.4, 1.3, one of CH=CH-CH<sub>2</sub>), 5.59 (1 H, app. dq, *J* 10.0, 2.1, one of CH=CH-CH<sub>2</sub>), 5.46 (1 H, app. dq, *J* 10.0, 2.1, one of CH=CH-CH<sub>2</sub>), 4.60 (1 H, dddd, *J* 9.7, 7.6, 6.0, 5.1, O-CH), 3.34 (1 H, dd, *J* 13.8, 5.1, one of S-CH<sub>2</sub>), 3.0 (1 H, dd, *J* 13.8, 7.6, one of S-CH<sub>2</sub>), 2.80 – 2.70 (1 H, m, one of ring CH<sub>2</sub>), 2.62 (1 H, app. dtt, *J* 23.4, 3.4, 2.1 one of ring CH<sub>2</sub>), 2.36 (1 H, dd, *J* 13.1, 6.0, one of CH<sub>2</sub>-Cq), 1.96 (1 H, dd, *J* 13.1, 9.7, one of CH<sub>2</sub>-Cq);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 177.0 (O-C=O), 134.7 (C<sub>q</sub>-S), 130.4 (2 × *o*-aromatic CH), 129.3 (2 × *m*-aromatic CH), 128.0 (*p*-aromatic CH or alkene CH), 127.3 (*p*-aromatic CH or alkene CH), 127.1 (*p*-aromatic CH or alkene CH), 125.5 (*p*-aromatic CH or alkene CH), 123.3 (*p*-aromatic CH or alkene CH), 75.5 (O-CH), 47.1 (ring C<sub>q</sub>), 43.3 (S-CH<sub>2</sub>), 38.9 (CH<sub>2</sub>-Cq), 26.0 (ring CH<sub>2</sub>); *m/z* (APCI) 273 (MH<sup>+</sup>, 100 %), 239 (14), 227 (18).

**1-(1-Hydroxymethyl-cyclohexa-2,5-dienyl)-3-phenylsulfanyl-propan-2-ol (200)**



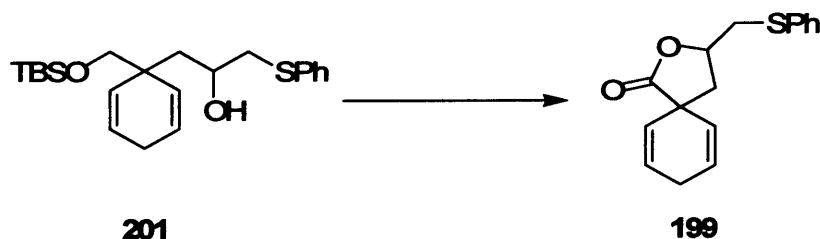
Lactone **199** (3.9 g, 14.3 mmol) in dry THF (5 ml) was carefully added to a stirred suspension of  $\text{LiAlH}_4$  (1.1 g, 29 mmol) in dry THF (25 ml) under a nitrogen atmosphere at room temperature in a flame-dried flask. After stirring for 24 h, 15 % aqueous NaOH solution (1.1 ml) was added carefully followed by water (3.5 ml) and the stirring was continued at room temperature for 18 hours. Filtration and concentration under reduced pressure afforded *the title diol* (3.3 g, 84 %) as an essentially-pure colourless oil;  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3383 (broad), 3015, 2920, 2805, 1632, 1582, 1480, 1438, 1039, 738;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.30 – 7.25 (2 H, m,  $2 \times$  *o*-aromatic CH), 7.23 – 7.17 (2 H, m,  $2 \times$  *m*-aromatic CH), 7.12 (1 H, app. tt,  $J$  7.2, 1.0, *p*-aromatic CH), 5.92 – 5.83 (2 H, m,  $2 \times$   $\text{CH}=\text{CH}-\text{CH}_2$ ), 5.53 (1 H, app. dq,  $J$  10.1, 2.0, one of  $\text{CH}=\text{CH}-\text{CH}_2$ ), 5.37 (1 H, app. dq,  $J$  10.1, 2.0, one of  $\text{CH}=\text{CH}-\text{CH}_2$ ), 3.79 (1 H, app. tt,  $J$  7.9, 4.0, O-CH), 3.30 (2 H, s, O- $\text{CH}_2$ ), 3.02 (1 H, dd,  $J$  13.6, 4.4, one of S- $\text{CH}_2$ ), 2.81 (1 H, dd,  $J$  13.6, 8.1, one of S- $\text{CH}_2$ ), 2.65 – 2.48 (2 H, m, ring  $\text{CH}_2$ ), 1.59 (1 H, dd,  $J$  14.2, 7.7, one of  $\text{CH}_2-\text{Cq}$ ), 1.52 (1 H, dd,  $J$  14.2, 3.5, one of  $\text{CH}_2-\text{Cq}$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 135.5 ( $\text{C}_q-\text{S}$ ), 129.8 (alkene CH), 129.7 ( $2 \times$  *o*-aromatic CH), 129.0 ( $2 \times$  *m*-aromatic CH), 127.8 (*p*-aromatic CH or alkene CH), 127.3 (*p*-aromatic CH or alkene CH), 126.4 ( $2 \times$  alkene CH), 70.3 (O- $\text{CH}_2$ ), 67.2 (O-CH), 43.7 (S- $\text{CH}_2$ ), 42.1 ( $\text{CH}_2-\text{Cq}$ ), 42.0 (ring  $\text{C}_q$ ), 26.5 (ring  $\text{CH}_2$ ).

**1-[1-(*t*-Butyldimethylsilyloxymethyl)-cyclohexa-2,5-dienyl]-3-phenylsulfanyl-propan-2-ol (201)**



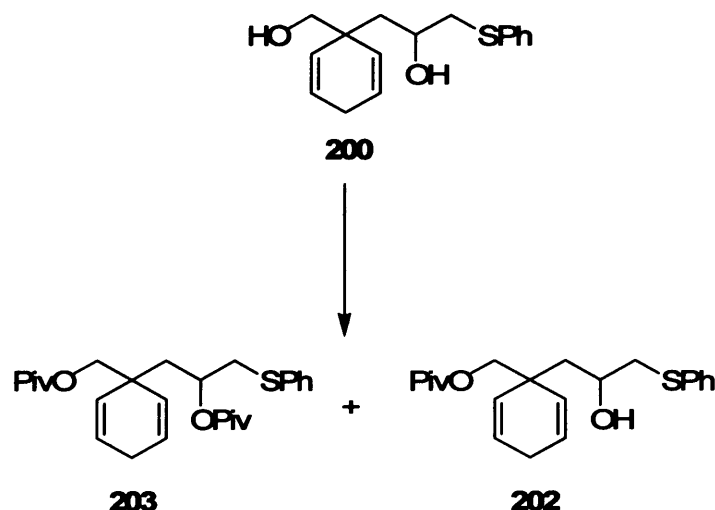
*t*-Butyldimethylchlorosilane (463.5 mg, 3.1 mmol, 1.7 equiv.) was added to a solution of diol **200** (0.5 g, 1.8 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (25 ml). Triethylamine (0.43 ml, 3.1 mmol, 1.7 equiv.) and DMAP (few crystals) were added. After stirring the resulting mixture at room temperature for 66 hours, aqueous 2 M HCl solution (20 ml) was added and the organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 15 ml). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford a yellow oil which was purified by flash column chromatography (eluting with CH<sub>2</sub>Cl<sub>2</sub>) to afford the *title compound* (367 mg, 52 %) as a pale yellow oil (Found: MH<sup>+</sup> 391.2121. C<sub>22</sub>H<sub>35</sub>O<sub>2</sub>SSi requires M, 391.2122);  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3418 (broad), 3019, 2953, 2928, 2855, 1584, 1471, 1253, 1106, 838, 776, 737;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.34 – 7.30 (2 H, m, 2 × *o*-aromatic CH), 7.27 – 7.21 (2 H, m, 2 × *m*-aromatic CH), 7.15 (1 H, app. tt, *J* 7.3, 1.2, *p*-aromatic CH), 5.84 – 5.74 (2 H, m, 2 × CH=CH-CH<sub>2</sub>), 5.64 (1 H, app. dq, *J* 10.2, 2.0, one of CH=CH-CH<sub>2</sub>), 5.43 (1 H, app. dq, *J* 10.2, 1.9, one of CH=CH-CH<sub>2</sub>), 3.89 – 3.81 (1 H, m, O-CH), 3.38 (2 H, s, O-CH<sub>2</sub>), 3.03 (1 H, dd, *J* 13.3, 5.0, one of S-CH<sub>2</sub>), 2.93 (1 H, dd, *J* 13.3, 7.4, one of S-CH<sub>2</sub>), 2.67 – 2.52 (2 H, m, ring CH<sub>2</sub>), 1.76 (1 H, dd, *J* 14.3, 3.9, one of CH<sub>2</sub>-Cq), 1.70 (1 H, dd, *J* 14.3, 7.6, one of CH<sub>2</sub>-Cq), 0.86 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>), 0.00 (6 H, s, 2 × CH<sub>3</sub>-Si);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 136.2 (C<sub>q</sub>-S), 130.4 (alkene CH), 130.2 (2 × *o*-aromatic CH), 129.3 (2 × *m*-aromatic CH), 129.0 (*p*-aromatic CH or alkene CH), 126.0 (2 × alkene CH), 125.5 (*p*-aromatic CH or alkene CH), 71.3 (O-CH<sub>2</sub>), 67.8 (O-CH), 44.1 (S-CH<sub>2</sub>), 41.7 (CH<sub>2</sub>-Cq), 41.2 (ring C<sub>q</sub>), 26.7 (ring CH<sub>2</sub>), 25.9 (C(CH<sub>3</sub>)<sub>3</sub>), 18.3 (C<sub>q</sub>-Si), -5.4 (2 × CH<sub>3</sub>-Si); *m/z* (EI) 390 (M<sup>+</sup>, 16 %), 334 (24), 333 (100), 316 (10), 315 (46), 301 (36), 297 (10), 267 (90).

#### Attempted Allylic Oxidation of Mono-Silyl Ether **201**



Celite (0.41 g) was added to a suspension of silyl ether **112** (100 mg, 0.26 mmol) in dry benzene (20 ml) at 0 °C in a flame-dried flask. 5 - 6 M *t*-BuOOH in decane (0.31 ml, 1.55 mmol, 6.0 equiv.) was added followed by portion-wise addition of pyridinium dichromate (579 mg, 1.55 mmol, 6.0 equiv.). The reaction mixture was stirred at room temperature for 20 hours then diluted with CH<sub>2</sub>Cl<sub>2</sub>. Filtration through a plug of celite and concentration under reduced pressure gave a dark brown oil. Purification by flash column chromatography (eluting with CH<sub>2</sub>Cl<sub>2</sub>) afforded lactone **199** (37 mg, 53 %). Data as reported on page 204.

### Protection of Diol **200** as the Mono- and Di-Pivaloate Esters



Pivaloyl chloride (1.3 ml, 10.5 mmol, 1.3 equiv.) was added to a solution of diol **200** (2.85 g, 7.9 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (25 ml). Triethylamine (1.4 ml, 10.5 mmol, 1.3 equiv.) and DMAP (few crystals) were added. After stirring at room temperature for 18 hours, aqueous 2 M HCl solution (20 ml) was added and the organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 30 ml). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford a yellow oil which was purified by flash chromatography (eluting with ethyl acetate-hexane 1.5:8.5) to afford the pure di-pivaloate ester **203** and mono-pivaloate ester **202** respectively:

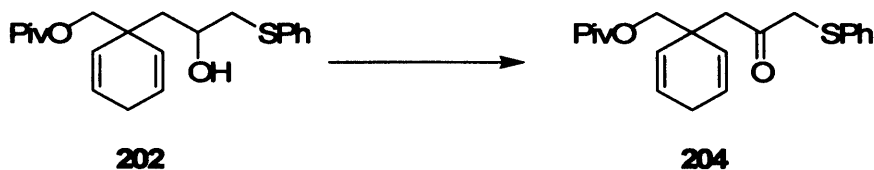
**2,2-Dimethyl-propionic acid 1-[2-(2,2-dimethyl-propionyloxy)-3-phenylsulfanyl-propyl]-cyclohexa-2,5-dienylmethyl ester (203)**: Pale yellow oil (185 mg, 4 %);  $\nu_{\text{max}}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3018, 2971, 2872, 2816, 1728, 1584, 1480, 1281, 1153, 1033,

739;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.30 – 7.27 (2 H, m, 2  $\times$  *o*-aromatic CH), 7.23 – 7.17 (2 H, m, 2  $\times$  *m*-aromatic CH), 7.13 – 7.07 (1 H, m, *p*-aromatic CH), 5.70 – 5.61 (2 H, m, 2  $\times$  CH=CH-CH<sub>2</sub>), 5.35 (1 H, app. dq, *J* 10.4, 2.0, one of CH=CH-CH<sub>2</sub>), 5.24 (1 H, app. dq, *J* 10.4, 2.0, one of CH=CH-CH<sub>2</sub>), 4.97 – 4.90 (1 H, m, O-CH), 3.77 (2 H, s, O-CH<sub>2</sub>), 3.03 (1 H, dd, *J* 13.6, 5.5, one of S-CH<sub>2</sub>), 2.88 (1 H, dd, *J* 13.6, 7.0, one of S-CH<sub>2</sub>), 2.47 – 2.42 (2 H, m, ring CH<sub>2</sub>), 1.82 (1 H, dd, *J* 14.5, 3.3, one of CH<sub>2</sub>-C<sub>q</sub>), 1.71 (1 H, dd, *J* 14.5, 7.4, one of CH<sub>2</sub>-C<sub>q</sub>), 1.12 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.08 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 178.3 (C=O), 177.6 (C=O), 135.8 (C<sub>q</sub>-S), 129.3 (2  $\times$  *o*-aromatic CH), 128.9 (2  $\times$  *m*-aromatic CH), 128.6 (*p*-aromatic CH or alkene CH), 128.5 (*p*-aromatic CH or alkene CH), 127.3 (*p*-aromatic CH or alkene CH), 126.1 (*p*-aromatic CH or alkene CH), 126.0 (*p*-aromatic CH or alkene CH), 70.6 (O-CH<sub>2</sub>), 69.7 (O-CH), 40.1 (S-CH<sub>2</sub>), 40.0 (ring C<sub>q</sub>), 38.9 (C(CH<sub>3</sub>)<sub>3</sub>), 38.6 (C(CH<sub>3</sub>)<sub>3</sub>), 38.1 (CH<sub>2</sub>-C<sub>q</sub>), 27.2 (C(CH<sub>3</sub>)<sub>3</sub>), 27.1 (C(CH<sub>3</sub>)<sub>3</sub>), 26.3 (ring CH<sub>2</sub>).

**2,2-Dimethyl-propionic acid 1-(2-hydroxy-3-phenylsulfanyl-propyl)-cyclohexa-2,5-dienylmethyl ester (202):** Colourless oil (1.3 g, 35 %);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3018, 2971, 2925, 2865, 2816, 1727, 1584, 1480, 1283, 1160, 1035, 738;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.30 – 7.25 (2 H, m, 2  $\times$  *o*-aromatic CH), 7.23 – 7.17 (2 H, m, 2  $\times$  *m*-aromatic CH), 7.14 – 7.09 (1 H, m, *p*-aromatic CH), 5.85 – 5.76 (2 H, m, 2  $\times$  CH=CH-CH<sub>2</sub>), 5.55 (1 H, app. dq, *J* 10.1, 2.0, one of CH=CH-CH<sub>2</sub>), 5.34 (1 H, app. dq, *J* 10.1, 2.0, one of CH=CH-CH<sub>2</sub>), 3.80 – 3.75 (3 H, m, O-CH and O-CH<sub>2</sub>), 3.01 (1 H, dd, *J* 13.5, 4.7, one of S-CH<sub>2</sub>), 2.84 (1 H, dd, *J* 13.5, 7.7, one of S-CH<sub>2</sub>), 2.63 – 2.45 (3 H, m, ring CH<sub>2</sub> and OH), 1.68 – 1.57 (2 H, m, CH<sub>2</sub>-C<sub>q</sub>), 1.10 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 178.3 (C=O), 135.7 (C<sub>q</sub>-S), 129.6 (alkene CH), 129.6 (2  $\times$  *o*-aromatic CH), 129.0 (2  $\times$  *m*-aromatic CH), 128.9 (*p*-aromatic CH or alkene CH), 126.9 (*p*-aromatic CH or alkene CH), 126.8 (*p*-aromatic CH or alkene CH), 126.3 (*p*-aromatic CH or alkene CH), 70.6 (O-CH<sub>2</sub>), 67.6 (O-CH), 43.4 (S-CH<sub>2</sub>), 41.9 (CH<sub>2</sub>-C<sub>q</sub>), 40.1 (ring C<sub>q</sub>), 38.9 (C(CH<sub>3</sub>)<sub>3</sub>), 27.2 (C(CH<sub>3</sub>)<sub>3</sub>), 26.4 (ring CH<sub>2</sub>).



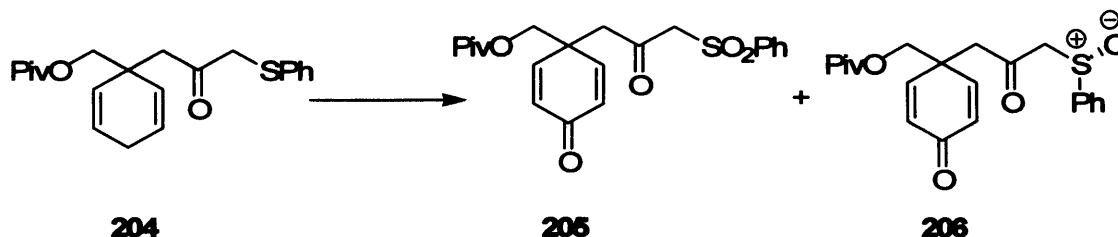
**2,2-Dimethyl-propionic acid 1-(2-oxo-3-phenylsulfanyl-propyl)-cyclohexa-2,5-dienylmethyl ester (204)**



IBX (1.56 g, 5.57 mmol, 3.06 equiv.) in DMSO (10 ml) was stirred at room temperature until a clear solution was obtained (*ca* 30 min.). A solution of alcohol **202** (0.66 g, 1.83 mmol) in DMSO (2 ml) was added and the mixture was stirred 6 h. Water (2 ml) was added and the mixture was stirred for 10 min, then cooled to 0 °C and stirred for 45 min. The mixture was partitioned between water (50 ml) and diethyl ether (50 ml) and the organic material was extracted into the ethereal layer. The ethereal extracts were washed several times with water. The combined ethereal extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford compound **204** (359 mg, 55 %) as an essentially-pure yellow oil;  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 2976, 2912, 1722, 1437, 1283, 1158, 1056, 952;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.26 – 7.11 (5 H, m, 5 × aromatic CH), 5.78 (2 H, app. dt, *J* 10.3, 3.3, 2 × CH=CH-CH<sub>2</sub>), 5.51 (2 H, app. dt, *J* 10.3, 2.0, 2 × CH=CH-CH<sub>2</sub>), 3.88 (2 H, s, O-CH<sub>2</sub>), 3.58 (2 H, s, S-CH<sub>2</sub>), 2.65 (2 H, s, CH<sub>2</sub>-C<sub>q</sub>), 2.57 – 2.52 (2 H, m, ring CH<sub>2</sub>), 1.10 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 203.2 (C=O), 178.0 (O-C=O), 134.8 (C<sub>q</sub>-S), 129.6 (2 × *o*-aromatic CH), 129.1 (2 × *m*-aromatic CH), 127.9 (2 × alkene CH), 126.8 (2 × alkene CH), 126.8 (*p*-aromatic CH), 69.9 (O-CH<sub>2</sub>), 47.8 (S-CH<sub>2</sub>), 45.2 (CH<sub>2</sub>-C<sub>q</sub>), 39.8 (ring C<sub>q</sub>), 38.9 (C(CH<sub>3</sub>)<sub>3</sub>), 27.2 (C(CH<sub>3</sub>)<sub>3</sub>), 26.3 (ring CH<sub>2</sub>).

## Attempted Allylic Oxidation of Compound 204

### 1. Using Pyridinium Dichromate/5 – 6 M *t*-BuOOH in decane

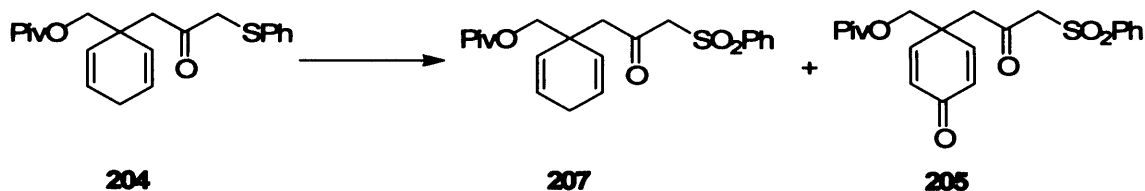


Celite (1.0 g) was added to a cooled (0 °C) suspension of substrate **204** (232 mg, 0.65 mmol) in dry benzene (10 ml) in a flame-dried flask. 5 - 6 M *t*-BuOOH in decane (0.55 ml, 2.75 mmol, 4.2 equiv.) was added. This was followed by portion-wise addition of pyridinium dichromate (1.0 g, 2.66 mmol, 4.1 equiv.) over 10 min. The resulting mixture was stirred at room temperature for 18 hours. After dilution with CH<sub>2</sub>Cl<sub>2</sub> and filtration through plug of celite, the combined solutions were concentrated *in vacuo* to afford a brown oil which was purified by flash chromatography (eluting with ethyl acetate-hexane in gradient mode from 2:1 to 9:1) to afford compound **205** and compound **206** respectively.

**2,2-Dimethyl-propionic acid 1-(3-benzenesulfonyl-2-oxo-propyl)-4-oxo-cyclohexa-2,5-dienylmethyl ester (205):** Yellow oil (12 mg, 5 %);  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.80 – 7.75 (2 H, m, 2  $\times$  *o*-aromatic CH), 7.68 – 7.62 (1 H, m, *p*-aromatic CH), 7.56 – 7.48 (2 H, m, 2  $\times$  *m*-aromatic CH), 6.85 (2 H, d, *J* 10.2, 2  $\times$   $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 6.31 (2 H, d, *J* 10.2, 2  $\times$   $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 4.17 (2 H, s, O-CH<sub>2</sub>), 4.03 (2 H, s, CH<sub>2</sub>-SO<sub>2</sub>), 3.08 (2 H, s, CH<sub>2</sub>-C<sub>q</sub>), 1.09 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) (not all quaternary carbon atoms observed due to small sample quantity) 193.9 (C=O), 148.5 (2  $\times$   $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 134.7 (*p*-aromatic CH), 131.2 (2  $\times$   $\text{CH}=\text{CH}-\text{C}=\text{O}$ ), 129.6 (2  $\times$  *o*-aromatic CH), 128.2 (2  $\times$  *m*-aromatic CH), 67.6 (O-CH<sub>2</sub>), 66.0 (CH<sub>2</sub>-SO<sub>2</sub>), 48.0 ( $\text{CH}_2-\text{C}_q$ ), 39.7 (ring C<sub>q</sub>), 39.0 ( $\text{C}(\text{CH}_3)_3$ ), 27.2 ( $\text{C}(\text{CH}_3)_3$ ).

**2,2-Dimethyl-propionic acid 1-(3-benzenesulfinyl-2-oxo-propyl)-4-oxo-cyclohexa-2,5-dienylmethyl ester (206):** Yellow oil (6.3 mg, 3 %); Data as given below.

## 2. Using Jacobsen's catalyst/*N*-Methylmorpholine-*N*-oxide/*m*-CPBA



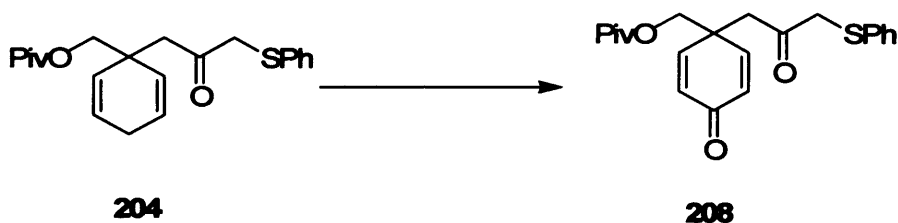
The Jacobsen's catalyst (*R,R*)-(-)-*N,N*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino manganese(III) chloride 98% (12.1 mg, 0.01 mmol) was added to a cooled (-30 °C) solution of cyclohexadiene **204** (67 mg, 0.19 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) under a nitrogen atmosphere. *N*-Methylmorpholine-*N*-oxide (167 mg, 1.43 mmol) was added followed by 50-55 % *m*-CPBA (98.4 mg, 0.57 mmol) and the resulting mixture was stirred for 24 h. The reaction was quenched with aqueous sodium sulfite (5 ml) and the organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 10 ml). The combined organic extracts were washed with sodium hydrogen carbonate (2 × 2 ml) and aqueous sodium sulfite (2 × 2 ml) then dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford a dark brown residue. Purification by flash chromatography (eluting with ethyl acetate-hexane 2:3) afforded sulfonyl diene **207** and sulfonyl dienone **205** respectively.

**2,2-Dimethyl-propionic acid 1-(3-benzenesulfonyl-2-oxo-propyl)-cyclohexa-2,5-dienylmethyl ester (207):** Yellow oil (24 mg, 32 %);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 2972, 1725, 1480, 1448, 1323, 1283, 1155, 1085, 731;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.28 – 7.77 (2 H, m, 2 × *o*-aromatic CH), 7.64 – 7.59 (1 H, m, *p*-aromatic CH), 7.54 – 7.47 (2 H, m, 2 × *m*-aromatic CH), 5.80 (2 H, app. dt, *J* 10.4, 3.3, 2 × CH=CH-CH<sub>2</sub>), 5.51 (2 H, app. dt, *J* 10.4, 1.9, 2 × CH=CH-CH<sub>2</sub>), 4.04 (2 H, s, O-CH<sub>2</sub>), 3.87 (2 H, s, CH<sub>2</sub>-SO<sub>2</sub>), 2.74 (2 H, s, C<sub>q</sub>-CH<sub>2</sub>), 2.63 – 2.43 (2 H, m, ring CH<sub>2</sub>), 1.13 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 196.4 (C=O), 178.1 (O-C=O), 138.6 (C<sub>q</sub>-S), 134.3 (*p*-aromatic CH), 129.3 (2 × *o*-aromatic CH), 128.4 (2 × *m*-aromatic CH or 2 × alkene CH), 127.6 (2 × *m*-aromatic CH or 2 × alkene CH), 127.2 (2 × *m*-aromatic CH or 2 × alkene CH), 69.8 (O-CH<sub>2</sub>), 67.8 (CH<sub>2</sub>-SO<sub>2</sub>), 51.2 (CH<sub>2</sub>-C<sub>q</sub>), 39.7 (ring C<sub>q</sub>), 39.0 (C(CH<sub>3</sub>)<sub>3</sub>), 27.2 (C(CH<sub>3</sub>)<sub>3</sub>), 26.3 (ring CH<sub>2</sub>).

**2,2-Dimethyl-propionic acid 1-(3-benzenesulfonyl-2-oxo-propyl)-4-oxo-cyclohexa-2,5-dienylmethyl ester (205):** Yellow oil (10 mg, 14 %); Data as given above.

### 3. Using Pyridinium Dichromate in Ethanol-Free Chloroform

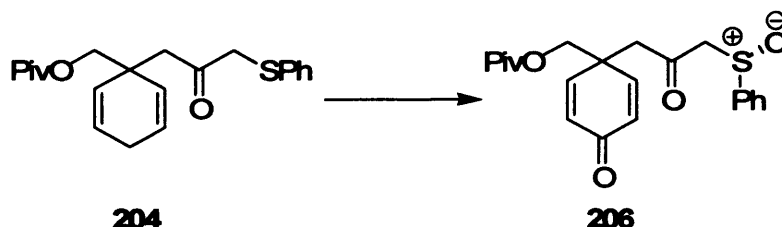
**2,2-Dimethyl-propionic acid 4-oxo-1-(2-oxo-3-phenylsulfanyl-propyl)-cyclohexa-2,5-dienylmethyl ester (208)**



Pyridinium dichromate (314.8 mg, 0.84 mmol, 3 equiv) and dry 4 Å molecular sieves (0.4 g) were added to a solution of cyclohexadiene **204** (0.1 g, 0.28 mmol) in ethanol-free chloroform (10 ml). The reaction mixture was heated under reflux for 9 hours then allowed to cool to room temperature. Dichloromethane was added and the resulting mixture was filtered through a short pad of celite. The resulting filtrate was concentrated under reduced pressure to afford a brown oil which was purified by flash column chromatography (eluting with ethyl acetate-hexane 2.5:1) to give compound **208** (17 mg, 16 %) as a brown oil (Found:  $MH^+$  373.1466.  $C_{21}H_{25}SO_4$  requires  $M$ , 373.1468);  $\nu_{max}$  (neat)/ $cm^{-1}$  3056, 2971, 2915, 1731, 1669, 1479, 1280, 1149, 1026;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 7.25 – 7.19 (5 H, m, 5  $\times$  aromatic CH), 6.78 (2 H, d,  $J$  10.2, 2  $\times$   $\underline{CH=CH-C=O}$ ), 6.23 (2 H, d,  $J$  10.2, 2  $\times$   $CH=\underline{CH-C=O}$ ), 4.15 (2 H, s, O- $\underline{CH_2}$ ), 3.52 (2 H, s,  $\underline{CH_2-S}$ ), 2.88 (2 H, s,  $C_q$ - $\underline{CH_2}$ ), 1.05 (9 H, s,  $C(CH_3)_3$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 201.1 ( $C=O$ ), 185.5 (conjugated  $C=O$ ), 177.0 (O- $C=O$ ), 149.2 (2  $\times$   $\underline{CH=CH-C=O}$ ), 135.4 ( $C_q-S$ ), 130.9 (2  $\times$   $CH=\underline{CH-C=O}$ ), 129.8 (2  $\times$   $o$ -aromatic CH), 129.4 (2  $\times$   $m$ -aromatic CH), 127.4 ( $p$ -aromatic CH), 66.1 (O- $\underline{CH_2}$ ), 44.4 ( $\underline{CH_2-S}$ ), 44.1 ( $\underline{CH_2-C_q}$ ), 38.9 (ring  $C_q$  and  $\underline{C(CH_3)_3}$ ), 27.1 ( $C(\underline{CH_3})_3$ );  $m/z$  (APCI) 373 ( $MH^+$ , 31 %), 345 (20), 343 (94), 271 (53), 260 (22), 259 (100), 241 (14), 191 (20), 166 (16), 126 (14), 121 (20).

#### 4. Using Pyridinium Dichromate/70 % *t*-BuOOH in Water

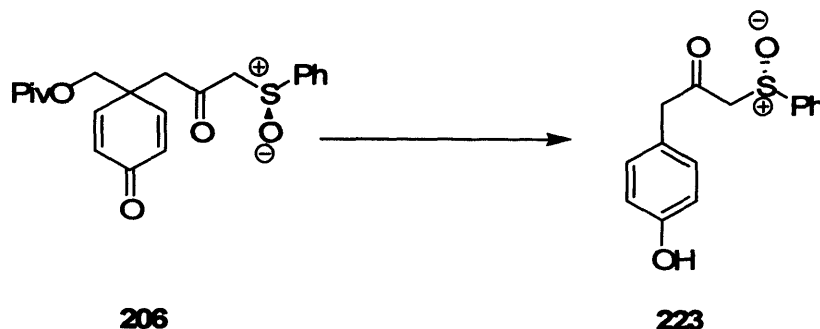
**2,2-Dimethyl-propionic acid 1-(3-benzenesulfinyl-2-oxo-propyl)-4-oxo-cyclohexa-2,5-dienylmethyl ester (206)**



Pyridinium dichromate (1.3 g, 3.46 mmol, 3.06 equiv.) was added to a cooled (-20 °C) solution of cyclohexadiene **204** (404 mg, 1.13 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml). 70 % *t*-BuOOH in water (3.02 ml, 4.92 mmol, 4.35 equiv.) was added. The resulting mixture was stirred for 48 hours, diluted with ethyl acetate and filtered through a pad of celite/sodium sulfate. The filtrate was concentrated under reduced pressure to afford a brown oil. Purification by flash chromatography (eluting with ethyl acetate-hexane 2:8) afforded compound **206** (101 mg, 23 %) as a viscous yellow oil;  $\nu_{\text{max}}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3046, 2973, 1725, 1667, 1627, 1479, 1280, 1147, 1039, 862;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.55 – 7.46 (5 H, m, 5 × aromatic CH), 6.82 – 6.76 (2 H, m, 2 × CH=CH-C=O), 6.29 – 6.23 (2 H, m, 2 × CH=CH-C=O), 4.15 and 4.11 (2 H, AB quartet, *J* 10.7, 2 × O-CH<sub>2</sub>), 3.74 (1 H, d, *J* 13.0, one of S-CH<sub>2</sub>), 3.61 (1 H, d, *J* 13.0, one of S-CH<sub>2</sub>), 2.83 and 2.74 (2 H, AB quartet, *J* 17.6, 2 × C<sub>q</sub>-CH<sub>2</sub>), 1.06 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 197.1 (C=O), 185.3 (conjugated C=O), 177.7 (O-C=O), 148.8 (2 × CH=CH-C=O), 141.8 (C<sub>q</sub>-SO), 131.9 (*p*-aromatic CH), 131.1 (one of CH=CH-C=O), 131.0 (one of CH=CH-C=O), 129.6 (2 × *o*-aromatic CH), 124.0 (2 × *m*-aromatic CH), 67.0 (O-CH<sub>2</sub>), 65.9 (CH<sub>2</sub>-SO), 49.4 (CH<sub>2</sub>-C<sub>q</sub>), 34.9 (ring C<sub>q</sub>), 38.9 (C(CH<sub>3</sub>)<sub>3</sub>), 27.1 (C(CH<sub>3</sub>)<sub>3</sub>); *m/z* (APCI) 389 (MH<sup>+</sup> + O, 68 %), 359 (100), 287 (28), 275 (33), 233 (64), 161 (19), 125 (28).

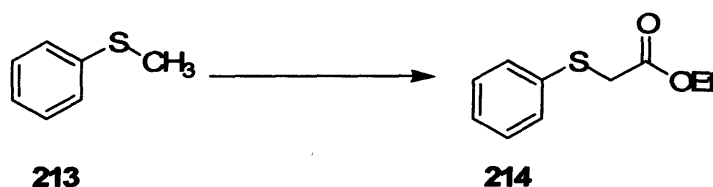
## Attempted Cyclisation of Sulfinyl dienone **206**

### 1-Benzenesulfinyl-3-(4-hydroxy-phenyl)-propan-2-one (**223**)



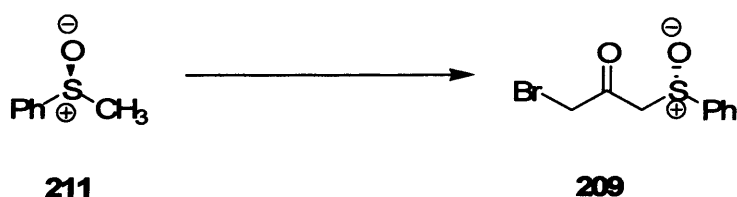
A solution of sulfinyl dienone **206** (83 mg, 0.22 mmol) in dry THF (3 ml) was added to a cooled (0 °C) suspension of sodium hydride (60 % dispersion in oil, 40 mg, 1.0 mmol, 4.5 equiv.) in dry THF (10 ml) under a nitrogen atmosphere. The resulting mixture was stirred for one hour at 0 °C then at room temperature for 17 hours. The reaction mixture was quenched with saturated ammonium chloride solution (10 ml) and the organic material extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 x 20 ml). The combined organic extracts were concentrated under reduced pressure to afford a yellow residue. Purification by flash chromatography (eluting with ethyl acetate-hexane 8:2) afforded compound **223** (38 mg, 65 %) as yellow oil;  $\nu_{\text{max}}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3347 (broad), 2956, 2915, 2855, 1710, 1515, 1445, 1260, 1087, 1028;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.59 – 7.54 (2 H, m, 2 × aromatic CH), 7.49 – 7.43 (3 H, m, 3 × aromatic CH), 6.88 (2 H, d, *J* 8.4, 2 × CH=CH-C-OH), 6.69 (2 H, app. d, *J* 8.4, 2 × CH=CH-C-OH), 3.85 (1 H, d, *J* 13.9, one of CH<sub>2</sub>-SO), 3.73 (1 H, d, *J* 13.9, one of CH<sub>2</sub>-SO), 3.62 and 3.56 (2 H, AB quartet, *J* 15.9, 2 × C<sub>q</sub>-CH<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 199.6 (C=O), 155.3 (C<sub>q</sub>-OH), 142.6 (C<sub>q</sub>-SO), 131.8 (aromatic CH), 130.8 (2 × aromatic CH), 124.0 (aromatic CH), 128.6 (aromatic C<sub>q</sub>-CH<sub>2</sub>), 124.2 (2 × aromatic CH), 115.9 (2 × aromatic CH), 66.7 (CH<sub>2</sub>-SO), 50.9 (CH<sub>2</sub>-C=O).

### Phenylsulfanyl-acetic acid ethyl ester (**214**)



Thioanisole **213** (2.1 g, 2.0 ml, 16.9 mmol) was added to a solution of DABCO (2 g, 17.8 mmol, 1.05 equiv.) in dry THF (30 ml) and under a nitrogen atmosphere. The resulting suspension was cooled to 0 °C and *n*-butyllithium (2.5 M solution in hexane, 9.3 ml, 23.25 mmol, 1.38 equiv.) was added. After removal of the cooling bath the resulting mixture was stirred at room temperature for one hour. The resulting white suspension was then cooled to -78 °C and ethyl 2-bromoacetate **212** (9.2 g, 6.1 ml, 55.1 mmol, 3.26 equiv) was added. The reaction mixture was allowed to warm to room temperature and stirring was continued for 18 hours. Saturated ammonium chloride solution (20 ml) was added and the product was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 ml). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford compound **214** (2.9 g, 94 %) as an essentially-pure yellow oil;  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3060, 2981, 1732, 1584, 1482, 1440, 1272, 1152, 1026, 911;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.31 – 7.26 (2 H, m, 2 × *o*-aromatic CH), 7.20 – 7.14 (2 H, m, 2 × *m*-aromatic CH), 7.10 (1 H, app. tt, *J* 7.4, 1.2, *p*-aromatic CH), 4.04 (2 H, q, *J* 7.2, O-CH<sub>2</sub>), 3.51 (2 H, s, S-CH<sub>2</sub>), 1.09 (3 H, t, *J* 7.2, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 169.7 (C=O), 135.0 (C<sub>q</sub>-S), 130.0 (2 × *o*-aromatic CH), 129.0 (2 × *m*-aromatic CH), 127.0 (*p*-aromatic CH), 61.6 (O-CH<sub>2</sub>), 36.7 (S-CH<sub>2</sub>), 14.1 (CH<sub>3</sub>).

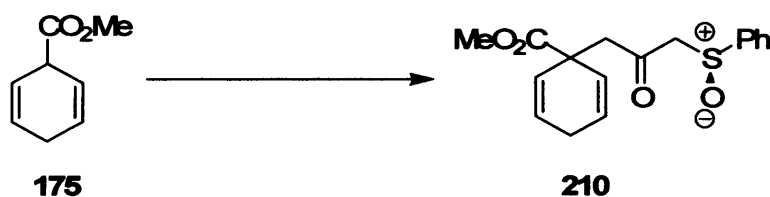
#### 1-Benzenesulfinyl-3-bromo-propan-2-one (**209**)



*n*-Butyllithium (2.5 M solution in hexane, 1.6 ml, 4 mmol, 2.0 equiv.) was added to freshly distilled *i*-Pr<sub>2</sub>NH (0.6 ml, 4.2 mmol, 2.1 equiv.) at room temperature under a nitrogen atmosphere. The mixture was stirred for 5 min. and dry THF (5 ml) was added. After cooling the resulting solution of LDA to -78 °C, a solution of methyl phenyl sulfoxide **211** (560 mg, 4.0 mmol, 2 equiv.) in dry THF (5 ml) was added and stirring was continued for one hour. Ethyl 2-bromoacetate **212** (0.22 ml, 2.0 mmol, 1 equiv) in dry THF (2 ml) was added and the reaction mixture was stirred for 45 min. at -78 °C. Saturated ammonium chloride solution (10 ml) was added and the product

was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 ml). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford a reddish yellow oil which was purified by flash column chromatography (eluting with hexane-ethyl acetate 1:2) to afford the *title compound* (447 mg, 43 %) as an off-white crystalline solid m.p. 92 – 94 °C (Found: MH<sup>+</sup> 260.9581. C<sub>9</sub>H<sub>10</sub><sup>79</sup>BrSO<sub>2</sub> requires M, 260.9579);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 1724, 1444, 1387, 1353, 1030, 740;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.61 – 7.55 (2 H, m, aromatic CH), 7.52 – 7.44 (3 H, m, aromatic CH), 4.06 (1 H, d, *J* 13.4, one of CH<sub>2</sub>-SO), 3.92 (1 H, d, *J* 13.4, one of CH<sub>2</sub>-SO), 3.91 (1 H, d, *J* 13.0, one of Br-CH<sub>2</sub>), 3.85 (1 H, d, *J* 13.0, one of Br-CH<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 192.7 (C=O), 142.1 (C<sub>q</sub>-S), 132.0 (*p*-aromatic CH), 129.7 (2 × *o*-aromatic CH), 124.0 (2 × *m*-aromatic CH), 64.5 (CH<sub>2</sub>-SO), 36.0 (Br-CH<sub>2</sub>); *m/z* (APCI) 263 (M<sup>+</sup> (<sup>81</sup>Br), 99 %), 261 (<sup>79</sup>Br, 100), 219 (17), 217 (30), 183 (25).

**1-(3-Benzensulfinyl-2-oxo-propyl)-cyclohexa-2,5-dienecarboxylic acid methyl ester (210)**



*n*-Butyllithium (2.5 M solution in hexane, 3.06 ml, 7.66 mmol, 2.0 equiv.) was added to freshly-distilled *i*-Pr<sub>2</sub>NH (0.80 g, 1.12 ml, 804 mmol, 2.1 equiv.) at room temperature under a nitrogen atmosphere. THF (5 ml) was added and the mixture was stirred for 30 min., then cooled to -78 °C. A solution of ester **175** (1.1 g, 7.66 mmol, 2 equiv.) in dry THF (5 ml) was added and stirring was continued for one hour. 1-benzenesulfinyl-3-bromo-propan-2-one **209** (1.0 g, 3.83 mmol) in dry THF (5 ml) was added and the reaction mixture was stirred for one hour at the same temperature. Saturated ammonium chloride solution (10 ml) was added and the product was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford a brown oil which was purified by flash column chromatography (eluting with hexane-ethyl acetate 1:1) to afford the *title compound* (683 mg, 27 %) as a viscous yellow oil (Found: MH<sup>+</sup> 319.0999. C<sub>17</sub>H<sub>19</sub>SO<sub>4</sub> requires M, 319.0999);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3026, 2946, 2995, 1714, 1443, 1388, 1217, 1088, 1037, 747;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.59 –

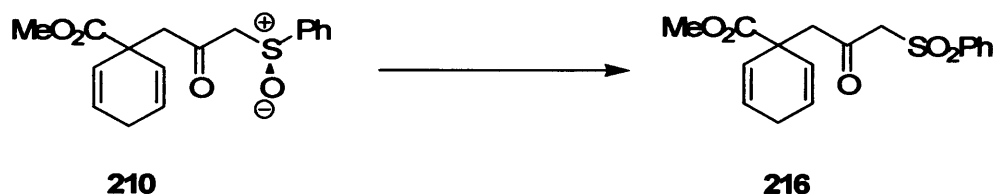


7.54 (2 H, m, aromatic CH), 7.50 – 7.43 (3 H, m, aromatic CH), 5.84 – 5.75 (2 H, m,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 5.65 (1 H, app. dq,  $J$  10.4, 2.0, one of  $\text{CH}=\text{CH}-\text{CH}_2$ ), 5.57 (1 H, app. dq,  $J$  10.4, 2.0, one of  $\text{CH}=\text{CH}-\text{CH}_2$ ), 3.75 and 3.71 (2 H, AB quartet,  $J$  13.7,  $2 \times \text{CH}_2-\text{SO}$ ), 3.60 (3 H, s,  $\text{CH}_3$ ), 2.95 (1 H, d,  $J$  18.1, one of  $\text{C}_q-\text{CH}_2$ ), 2.85 (1 H, d,  $J$  18.1, one of  $\text{C}_q-\text{CH}_2$ ), 2.68 – 2.50 (2 H, m, ring  $\text{CH}_2$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 198.8 ( $\text{C}=\text{O}$ ), 174.0 ( $\text{O}-\text{C}=\text{O}$ ), 142.6 ( $\text{C}_q-\text{S}$ ), 131.7 ( $p$ -aromatic CH), 129.5 ( $2 \times o$ -aromatic CH), 126.6 (alkene CH), 126.5 (alkene CH), 126.1 ( $2 \times$  alkene CH), 124.1 ( $2 \times m$ -aromatic CH), 67.9 ( $\text{CH}_2-\text{SO}$ ), 54.7 ( $\text{CH}_2-\text{C}_q$ ), 52.7 ( $\text{CH}_3$ ), 45.4 (ring  $\text{C}_q$ ), 25.9 (ring  $\text{CH}_2$ );  $m/z$  (APCI) 319 ( $\text{MH}^+$  100 %), 251 (28), 275 (19), 217 (14), 139 (18).

### Attempted allylic oxidation of compound 210

#### 1. Using Jacobsen's catalyst/*N*-Methylmorpholine-*N*-oxide/*m*-CPBA

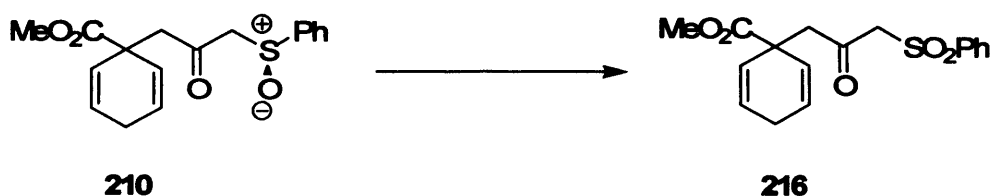
#### 1-(3-Benzensulfonyl-2-oxo-propyl)-cyclohexa-2,5-dienecarboxylic acid methyl ester (216)



Jacobsen's catalyst (*R,R*)-(-)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino manganese(III) chloride 98% (12.6 mg, 0.02 mmol, 0.1 equiv.) was added to a cooled (-30 °C) solution of compound **210** (63 mg, 0.19 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (10 ml) under a nitrogen atmosphere. *N*-Methylmorpholine-*N*-oxide (174 mg, 1.49 mmol, 7.5 equiv.) was added followed by 50-55 % *m*-CPBA (195.3 mg, 0.594 mmol, 3 equiv.) and the resulting mixture stirred for 24 h. The mixture was quenched with aqueous sodium sulfite (5 ml) and the organic material was extracted into  $\text{CH}_2\text{Cl}_2$  ( $2 \times 10$  ml). The combined organic extracts were washed with sodium hydrogen carbonate ( $2 \times 2$  ml) and aqueous sodium sulfite ( $2 \times 2$  ml) then dried over  $\text{MgSO}_4$ . The solvent was removed under reduced pressure to afford sulfonyl cyclohexadiene **216** (34 mg, 54 %) as a brown oil. Data are given below.

## 2. Using Pyridinium Dichromate in Ethanol-Free Chloroform

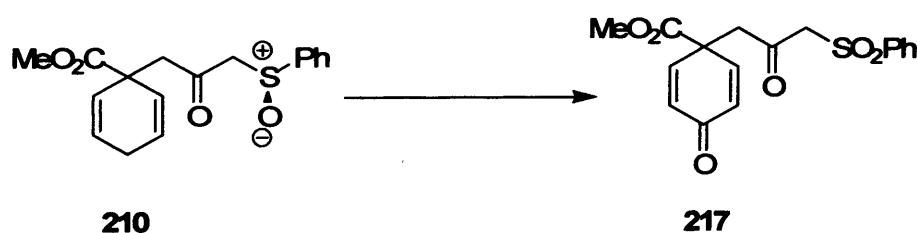
### 1-(3-Benzensulfonyl-2-oxo-propyl)-cyclohexa-2,5-dienecarboxylic acid methyl ester (216)



Pyridinium dichromate (357.4 mg, 0.95 mmol, 3.06 equiv) and dry 4 Å molecular sieves (0.45 g) were added to a solution of compound **210** (0.1 g, 0.314 mmol) in ethanol-free chloroform (15 ml). The reaction mixture was heated under reflux for 5 hours, then allowed to cool to room temperature. Dichloromethane (10 ml) was added and the resulting mixture was filtered through a short pad of celite. The filtrate was concentrated under reduced pressure to afford the sulfonyl cyclohexadiene **216** (29 mg, 28 %) as a somewhat impure brown oil;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.80 (2 H, d,  $J$  7.6, *o*-aromatic CH), 7.62 (1 H, t,  $J$  7.2, *p*-aromatic CH), 7.51 (2 H, app. t,  $J$  7.3, *m*-aromatic CH), 5.88 – 5.80 (2 H, m,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 5.69 – 5.57 (2 H, m,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 4.06 (2 H, s,  $\text{CH}_2-\text{SO}_2$ ), 3.59 (3 H, s,  $\text{CH}_3$ ), 3.11 (2 H, s,  $\text{C}_q-\text{CH}_2$ ), 2.71 – 2.54 (2 H, m, ring  $\text{CH}_2$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 195.5 (C=O), 173.9 (O-C=O), 138.3 ( $\text{C}_q-\text{SO}_2$ ), 134.4 (*p*-aromatic CH), 129.4 ( $2 \times$  *o*-aromatic CH), 128.4 ( $2 \times$  alkene CH), 126.8 ( $2 \times$  alkene CH), 125.8 ( $2 \times$  *m*-aromatic CH), 67.2 ( $\text{CH}_2-\text{SO}_2$ ), 53.9 ( $\text{CH}_2-\text{C}_q$ ), 52.7 ( $\text{CH}_3$ ), 45.4 (ring  $\text{C}_q$ ), 26.0 (ring  $\text{CH}_2$ ).

## 3. Using of Pyridinium Dichromate/5 – 6 M *t*-BuOOH

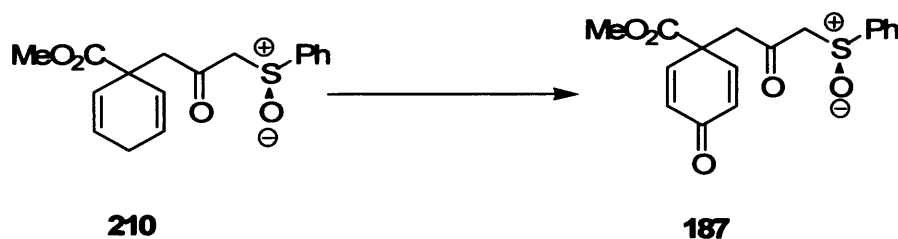
### 1-(3-Benzensulfonyl-2-oxo-propyl)-4-oxo-cyclohexa-2,5-dienecarboxylic acid methyl ester (217)



Celite (0.5 g) was added to a cooled (0 °C) suspension of compound **210** (100 mg, 0.314 mmol) in benzene (10 ml) in a flame-dried flask. 5 - 6 M *t*-BuOOH in decane (0.27 ml, 1.35 mmol, 4.3 equiv.) was added. This was followed by portion-wise addition of pyridinium dichromate (0.48 g, 1.28 mmol, 4.1 equiv.) over 5 min. The resulting mixture was stirred at 0 °C for one hour then at room temperature for 18 hours. After dilution with CH<sub>2</sub>Cl<sub>2</sub> and filtration through a pad of celite, the combined solutions were concentrated *in vacuo* to give a brown residue which was purified by flash column chromatography (eluting with hexane-ethyl acetate 7.5:2.5) to afford the pure sulfonyl cyclohexadienone **217** (3.1 mg, 3 %) as a yellow oil;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.81 (2 H, dd, *J* 7.3, 1.3, *o*-aromatic CH), 7.69 – 7.63 (1 H, m, *p*-aromatic CH), 7.57 – 7.51 (2  $\times$  *m*-aromatic CH), 6.88 (2 H, d, *J* 10.2, 2  $\times$  CH=CH-C=O), 6.32 (2 H, d, *J* 10.2, 2  $\times$  CH=CH-C=O), 4.10 (2 H, s, CH<sub>2</sub>-SO<sub>2</sub>), 3.65 (3 H, s, CH<sub>3</sub>), 3.28 (2 H, s, C<sub>q</sub>-CH<sub>2</sub>).

#### 4. Using Pyridinium Dichromate/70 % *t*-BuOOH in Water

##### 1-(3-Benzensulfinyl-2-oxo-propyl)-4-oxo-cyclohexa-2,5-dienecarboxylic acid methyl ester (**187**)

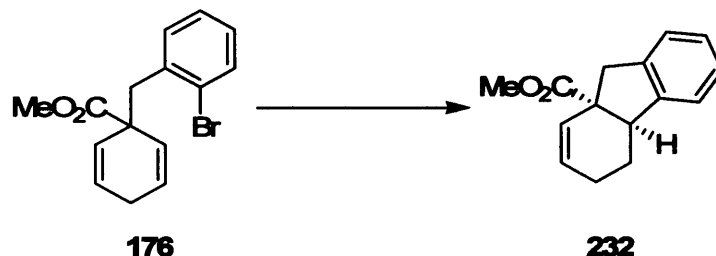


Pyridinium dichromate (362 mg, 0.96 mmol, 3.06 equiv.) was added to a cooled (-20 °C) solution of compound **210** (100 mg, 0.314 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 ml). 70 % *t*-BuOOH in water (0.13 ml, 0.212 mmol, 4.37 equiv.) was added. The resulting mixture was stirred at -20 °C for 48 hours, diluted with dichloromethane, and filtered through a pad of celite/sodium sulfate. The filtrate was concentrated under reduced pressure to afford a brown oil. Purification by flash column chromatography (eluting with ethyl acetate-hexane 8:2) afforded compound **187** (73 mg, 70 %) as a pale gum;  $\nu_{\text{max}}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3056, 2955, 1732, 1666, 1626, 1444, 1402, 1240, 1041, 863;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.55 – 7.45 (5 H, m, 5  $\times$  aromatic CH), 6.88 (1 H, app. dd, *J* 10.0, 2.2, one of CH=CH-C=O), 6.77 (1 H, app. dd, *J* 10.0, 2.2, one of CH=CH-C=O), 6.28 (1 H, broad d, *J* 10.2, one of CH=CH-C=O), 6.24 (1 H, broad d, *J* 10.2, one of

CH=CH-C=O), 3.83 (1 H, d,  $J$  12.9, one of CH<sub>2</sub>-SO), 3.68 (1 H, d,  $J$  12.9, one of CH<sub>2</sub>-SO), 3.63 (3 H, s, O-CH<sub>3</sub>), 3.08 and 2.97 (2 H, AB quartet,  $J$  18.7, 2 × C<sub>q</sub>-CH<sub>2</sub>);  
 $\delta_c$  (100 MHz; CDCl<sub>3</sub>) 197.3 (C=O), 184.7 (conjugated C=O), 170.0 (O-C=O), 145.9 (2 × CH=CH-C=O), 141.6 (C<sub>q</sub>-SO), 131.9 (*p*-aromatic CH), 130.7 (one of CH=CH-C=O), 130.4 (one of CH=CH-C=O), 129.6 (2 × *o*-aromatic CH), 124.0 (2 × *m*-aromatic CH), 66.3 (CH<sub>2</sub>-SO), 53.6 (CH<sub>3</sub>), 51.8 (CH<sub>2</sub>-C<sub>q</sub>), 49.2 (ring C<sub>q</sub>).

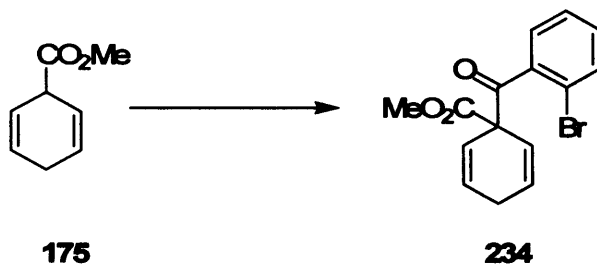
## 6.4. Experimental Data for Chapter 4

### (4*bRS*,8*aSR*)-4*b*,5,6,9-Tetrahydro-fluorene-8*a*-carboxylic acid methyl ester (232)<sup>64</sup>



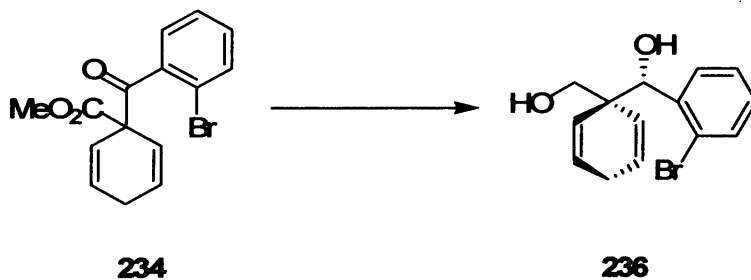
AIBN (169 mg, 1.03 mmol, 1.15 equiv.) was added to a solution of the bromide **176** (274 mg, 0.89 mmol, 1.0 equiv.) in dry benzene (20 ml). After heating the mixture to reflux, tributyltin hydride (0.27 ml, 1.03 mmol, 1.15 equiv.) was added dropwise and the resulting mixture was refluxed for 5 hours under a nitrogen atmosphere. The solvent was removed on a rotary evaporator and the residue was dissolved in ether and stirred with an excess of saturated aqueous potassium fluoride solution for 1 h. The organic material was extracted into Et<sub>2</sub>O (3 × 20 ml). The combined extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford the crude product as a yellow oil. Purification by flash column chromatography (eluting with ether-hexane 1:9) afforded the *title compound* (65 mg, 32 %) as a colourless oil (Found: MH<sup>+</sup>, 229.1226. C<sub>15</sub>H<sub>17</sub>O<sub>2</sub> requires M, 229.1223);  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3023, 2929, 1729, 1482, 1433, 1254, 1221, 1053, 814, 748;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.15 – 7.06 (4 H, m, aromatic CH), 5.69 (1 H, ddd, *J* 10.0, 4.7, 2.8, CH=CH-CH<sub>2</sub>), 5.56 (1 H, d, *J* 10.0, CH=CH-CH<sub>2</sub>), 3.75 (1 H, app. t, *J* 4.1, ring junction CH), 3.68 (3 H, s, O-CH<sub>3</sub>), 3.38 (1 H, d, *J* 15.7 one of CH<sub>2</sub>-C<sub>q</sub>), 2.89 (1 H, d, *J* 15.7 one of CH<sub>2</sub>-C<sub>q</sub>), 2.12 – 2.05 (1 H, m, one of CH<sub>2</sub>-CH<sub>2</sub>), 2.03 – 1.93 (1 H, m, one of CH<sub>2</sub>-CH<sub>2</sub>), 1.92 – 1.75 (2 H, m, two of CH<sub>2</sub>-CH<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 175.9 (O-C=O), 143.6 (aromatic C<sub>q</sub>), 140.8 (aromatic C<sub>q</sub>), 129.8 (aromatic or alkene CH), 128.5 (aromatic or alkene CH), 126.7 (aromatic or alkene CH), 126.4 (aromatic or alkene CH), 124.9 (aromatic or alkene CH), 123.0 (aromatic or alkene CH), 53.8 (ring junction C<sub>q</sub>), 52.3 (O-CH<sub>3</sub>), 45.2 (ring junction CH), 43.3 (CH<sub>2</sub>-C<sub>q</sub>), 21.8 (CH=CH-CH<sub>2</sub>), 20.5 (CH-CH<sub>2</sub>); *m/z* (APCI) 229 (MH<sup>+</sup>, 100 %).

**1-(2-Bromobenzoyl)-cyclohexa-2,5-dienecarboxylic acid methyl ester (234)**



According to the general procedure on page 192, compound **234** was obtained from ester **175** (7.0 g, 50.1 mmol, 1.0 equiv.) in dry THF (10 ml) and 2-bromobenzoyl chloride<sup>67</sup> (12.1 g, 55.1 mmol, 1.1 equiv) in THF (12 ml) as a brown waxy solid which was purified by flash chromatography (eluting with hexane-CH<sub>2</sub>Cl<sub>2</sub> 5.5:4.5) to afford the *title compound* (8.5 g, 52 %) as a pale yellow waxy solid m.p. 43 – 45 °C (Found: (M+NH<sub>4</sub>)<sup>+</sup> 338.0387. C<sub>15</sub>H<sub>17</sub>NO<sub>3</sub><sup>79</sup>Br requires M, 338.0386);  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3051, 2952, 2882, 1741, 1705, 1433, 1286, 1231, 1052, 922, 737;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.49 (1 H, d, *J* 7.4, one of aromatic CH), 7.24 – 7.14 (3 H, m, aromatic CH), 6.03 (2 H, broad d, *J* 10.2, 2 × alkene CH), 5.93 (2 H, broad d, *J* 10.2, 2 × alkene CH), 3.78 (3 H, s, O-CH<sub>3</sub>), 2.63 (1 H, broad d, *J* 23.5, one of ring CH<sub>2</sub>), 2.45 (1 H, broad d, *J* 23.5, one of ring CH<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 200.4 (C=O), 170.4 (O-C=O), 140.7 (aromatic C<sub>q</sub>-C=O), 133.0 (aromatic CH), 130.7 (aromatic CH), 128.6 (2 × alkene CH), 127.2 (aromatic CH), 126.5 (aromatic CH), 122.6 (2 × alkene CH), 118.7 (C<sub>q</sub>-Br), 62.7 (ring C<sub>q</sub>), 53.0 (O-CH<sub>3</sub>), 26.1 (ring CH<sub>2</sub>); *m/z* (APCI) 323 (M<sup>+</sup> (<sup>81</sup>Br), 96 %), 321 (M<sup>+</sup> (<sup>79</sup>Br), 100 %).

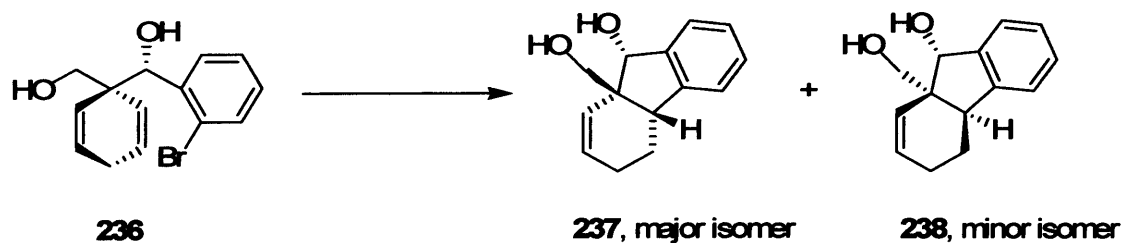
**1-(2-Bromophenyl)-(1-hydroxymethyl-cyclohexa-2,5-dienyl)-methanol (236)**



A solution of keto ester **234** (5.0 g, 15.5 mmol) in dry THF (10 ml) was carefully added to a stirred suspension of LiAlH<sub>4</sub> (1.8 g, 46.6 mmol) in dry THF (20 ml) under

a nitrogen atmosphere at room temperature in a flame-dried flask. After stirring for 7 h, 15 % aqueous NaOH solution (1.8 ml) was added carefully followed by water (5.3 ml) and the stirring was continued at room temperature for 18 hours. Filtration and concentration under reduced pressure afforded a viscous yellow oil. Purification by flash chromatography (eluting with hexane-ethyl acetate 7.5:2.5) afforded the *title diol* (2.5 g, 55 %) as a colourless viscous oil (Found:  $(M+NH_4)^+$ , 312.0596.  $C_{14}H_{19}NO_2^{79}Br$  requires  $M$ , 312.0594);  $\nu_{max}$  (neat)/ $cm^{-1}$  3374 (broad), 3025, 2878, 2814, 1469, 1435, 1020, 749;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 7.44 (1 H, dd,  $J$  7.9, 1.8, aromatic CH), 7.41 (1 H, dd,  $J$  8.0, 1.1, aromatic CH), 7.24 – 7.18 (1 H, m, aromatic CH), 7.03 (1 H, app. td,  $J$  7.6, 1.7, aromatic CH), 6.00 (1 H, app. dtd,  $J$  10.3, 3.3, 1.6, one of  $CH=CH-CH_2$ ), 5.83 (1 H, app. dq,  $J$  10.3, 2.0, one of  $CH=CH-CH_2$ ), 5.77 (1 H, app. dtd,  $J$  10.3, 3.3, 1.5, one of  $CH=CH-CH_2$ ), 5.56 (1 H, app. dq,  $J$  10.3, 2.0, one of  $CH=CH-CH_2$ ), 5.21 (1 H, s,  $CH-OH$ ), 3.79 (1 H, d,  $J$  10.5, one of  $CH_2-OH$ ), 3.49 (1 H, d,  $J$  10.5, one of  $CH_2-OH$ ), 2.49 (1 H, app. dtt,  $J$  23.1, 3.6, 1.8, one of ring  $CH_2$ ), 2.25 (1 H, app. double quintet,  $J$  23.1, 2.7, one of ring  $CH_2$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 139.9 (aromatic  $C_q$ ), 132.3 (alkene CH or aromatic CH), 130.2 (alkene CH or aromatic CH), 129.6 (alkene CH or aromatic CH), 129.0 (alkene CH or aromatic CH), 128.5 (alkene CH or aromatic CH), 126.9 (alkene CH or aromatic CH), 125.8 (alkene CH or aromatic CH), 125.4 (alkene CH or aromatic CH), 123.9 ( $C_q-Br$ ), 76.3 ( $CH-OH$ ), 69.2 ( $CH_2-OH$ ), 48.8 (ring  $C_q$ ), 26.7 (ring  $CH_2$ );  $m/z$  (APCI) 279 ( $M^+ - 17$  ( $^{81}Br$ ), 8 %), 277 ( $M^+ - 17$  ( $^{79}Br$ ), 12 %), 261 (100), 259 (99), 180 (53), 179 (13).

### Free radical cyclisation of bromide (236)



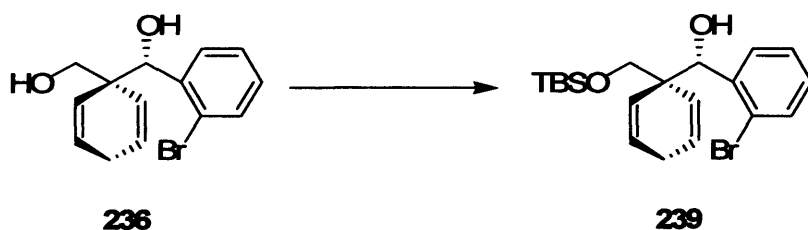
AIBN (306 mg, 1.86 mmol, 1.1 equiv.) was added to a solution of bromide **236** (0.5 g, 1.69 mmol) in dry benzene (30 ml). After heating the mixture to reflux, tributyltin hydride (0.45 ml, 1.69 mmol, 1.0equiv.) was added dropwise and the resulting mixture was refluxed for 5 hours under a nitrogen atmosphere. The solvent was

removed on a rotary evaporator to afford the crude product as a yellow oil. Purification by flash column chromatography over silica gel containing 10 % solid KF (eluting with ethyl acetate-hexane 1:9) afforded a mixture of two diastereoisomers **237** and **238** (70 mg, 19 %). From this mixture, the major isomer, **237**, was isolated (50 mg, 14 %) as a colourless solid.

**(4*aSR*,9*RS*,9*aSR*)-9*a*-Hydroxymethyl-4,4*a*,9,9*a*-tetrahydro-3*H*-fluoren-9-ol (**237**):**

Colourless solid (50 mg, 14 %), m.p. 108 – 110 °C (Found: (M+NH<sub>4</sub>)<sup>+</sup>, 234.1490. C<sub>14</sub>H<sub>20</sub>O<sub>2</sub>N requires M, 234.1489);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3419 (broad), 1120, 1090, 1051, 1017, 776, 745;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.32 (1 H, app. dd, *J* 8.1, 2.0, aromatic CH), 7.23 – 7.15 (3 H, m, aromatic CH), 6.03 – 5.97 (1 H, m, CH=CH-CH<sub>2</sub>), 5.64 (1 H, d, *J* 10.3, CH=CH-CH<sub>2</sub>), 4.99 (1 H, s, CH-OH), 3.69 (1 H, d, *J* 10.7, one of CH<sub>2</sub>-OH), 3.60 (1 H, d, *J* 10.7, one of CH<sub>2</sub>-OH), 3.14 (1 H, app. t, *J* 5.6, ring junction CH), 1.99 – 1.80 (4 H, m, CH<sub>2</sub>-CH<sub>2</sub>), 1.63 (2 H, broad resonance, 2 × OH);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 143.6 (aromatic C<sub>q</sub>), 143.6 (aromatic C<sub>q</sub>), 133.8 (aromatic or alkene CH), 128.2 (aromatic or alkene CH), 127.1 (aromatic or alkene CH), 124.8 (aromatic or alkene CH), 124.6 (aromatic or alkene CH), 123.5 (aromatic or alkene CH), 79.2 (CH-OH), 68.0 (CH<sub>2</sub>-OH), 54.3 (ring junction C<sub>q</sub>), 42.8 (ring junction CH), 23.8 (CH=CH-CH<sub>2</sub>), 22.1 (CH-CH<sub>2</sub>); *m/z* (APCI) 200 (M-OH, 10 %), 199 (66), 183 (17), 181 (100), 169 (70).

**1-(2-Bromophenyl)-[1-(*tert*-butyl-dimethylsilanyloxymethyl)-cyclohexa-2,5-dienyl]-methanol (**239**)**

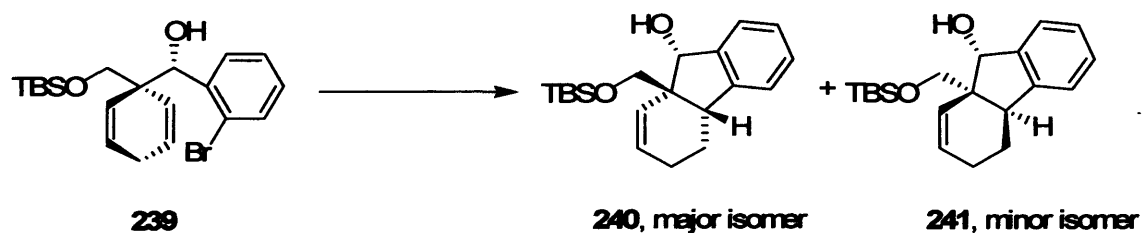


*t*-Butyldimethylchlorosilane (0.48 g, 3.2 mmol, 1.1 equiv.) was added to a solution of diol **236** (856 mg, 2.9 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 ml). Triethylamine (0.45 ml, 3.2 mmol, 1.1 equiv.) was added followed by DMAP (few crystals). The resulting mixture was stirred at room temperature under a nitrogen atmosphere for 24 h. then



quenched with aqueous 2 M HCl solution (10 ml). The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 ml). The combined extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford the *title compound* as an essentially-pure yellow oil (1.16 g, 97 %) (Found: MH<sup>+</sup> (<sup>79</sup>Br), 409.1197. C<sub>20</sub>H<sub>30</sub>O<sub>2</sub><sup>79</sup>BrSi requires M, 409.1193);  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3452 (broad), 3029, 2954, 2928, 2857, 1470, 1256, 1098, 1048, 1019, 837, 778, 745;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.40 (1 H, dd, *J* 7.8, 1.7, aromatic CH), 7.30 (1 H, dd, *J* 8.0, 1.2, aromatic CH), 7.11 (1 H, app. td, *J* 7.8, 1.0, aromatic CH), 6.93 (1 H, app. td, *J* 7.8, 1.7, aromatic CH), 5.83 (1 H, app. dq, *J* 10.4, 1.9, one of CH=CH-CH<sub>2</sub>), 5.78 (1 H, app. dtd, *J* 10.2, 3.2, 1.5, one of CH=CH-CH<sub>2</sub>), 5.56 (1 H, app. dq, *J* 10.2, 1.8, one of CH=CH-CH<sub>2</sub>), 5.45 (1 H, app. dtd, *J* 10.4, 3.0, 1.6, one of CH=CH-CH<sub>2</sub>), 5.35 (1 H, s, CH-OH), 3.69 (1 H, d, *J* 9.5, one of CH<sub>2</sub>-O), 3.61 (1 H, d, *J* 9.5, one of CH<sub>2</sub>-O), 2.30 (1 H, app. dtt, *J* 22.9, 3.7, 1.8, one of ring CH<sub>2</sub>), 1.95 (1 H, app. doubled quintet, *J* 22.9, 2.6, one of ring CH<sub>2</sub>), 0.82 (9 H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>), 0.01 (3 H, s, Si-CH<sub>3</sub>), 0.00 (3 H, s, Si-CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 140.5 (aromatic C<sub>q</sub>), 131.8 (aromatic or alkene CH), 130.1 (aromatic or alkene CH), 128.5 (aromatic or alkene CH), 127.5 (aromatic or alkene CH), 126.6 (aromatic or alkene CH), 126.5 (aromatic or alkene CH), 125.9 (aromatic or alkene CH), 125.0 (aromatic or alkene CH), 124.2 (C<sub>q</sub>-Br), 78.1 (CH-OH), 72.1 (CH<sub>2</sub>-OH), 46.8 (ring C<sub>q</sub>), 26.8 (ring CH<sub>2</sub>), 25.9 (3 × CH<sub>3</sub>), 18.2 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub>), -5.5 (Si-CH<sub>3</sub>), -5.6 (Si-CH<sub>3</sub>); *m/z* (APCI) 411 (M<sup>+</sup> (<sup>81</sup>Br) 91 %), 409 (88), 393 (23), 391 (24), 261 (73), 269 (70), 239 (100).

### Free radical cyclisation of bromide 239

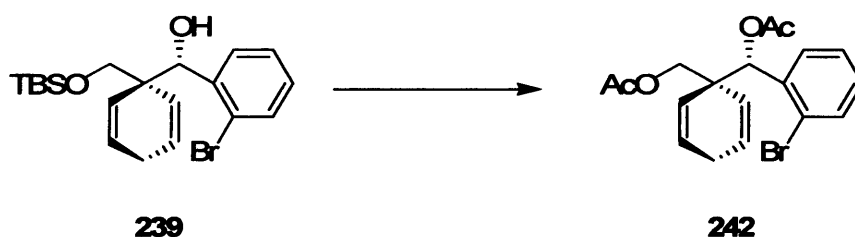


AIBN (186.8 mg, 1.34 mmol, 1.1 equiv.) was added to a solution of bromide 239 (423 mg, 1.03 mmol, 1.0 equiv.) in dry benzene (20 ml). After heating the mixture to reflux, tributyltin hydride (0.27 ml, 1.03 mmol, 1.0 equiv.) was added dropwise and the resulting mixture was refluxed for 5 hours under a nitrogen atmosphere. The solvent was removed on a rotary evaporator to afford the crude product as a yellow

oil. Purification by flash column chromatography over silica gel containing 10 % solid KF (eluting with ether-hexane 0.7:9.3) afforded a mixture of the major and the minor isomers (118 mg, 35 %) as a colourless oil and the major isomer (64 mg, 18 %) as a colourless oil.

**(4*aSR*,9*RS*,9*aSR*)-9*a*-(*tert*-Butyldimethylsilanyloxymethyl)-4,4*a*,9,9*a*-tetrahydro-3*H*-fluoren-9-ol (240) (major isomer):** Colourless oil (64 mg, 18.4 %);  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3424 (broad), 3025, 20928, 2855, 1462, 1389, 1256, 1105, 1052, 837, 778;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.34 – 7.30 (1 H, m, aromatic CH), 7.21 – 7.13 (3 H, m, aromatic CH), 5.83 (1 H, app. dt, *J* 10.3, 2.2, CH=CH-CH<sub>2</sub>), 5.62 (1 H, d, *J* 10.3, CH=CH-CH<sub>2</sub>), 5.19 (1 H, s, CH-OH), 3.66 (1 H, d, *J* 9.8, one of CH<sub>2</sub>-O), 3.56 (1 H, d, *J* 9.8, one of CH<sub>2</sub>-O), 3.12 (1 H, app. t, *J* 4.1, ring junction CH), 2.04 – 1.72 (4 H, m, CH<sub>2</sub>-CH<sub>2</sub>), 0.82 (9 H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>), 0.01 (3 H, s, Si-CH<sub>3</sub>), 0.00 (3 H, s, Si-CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 144.1 (aromatic C<sub>q</sub>), 143.4 (aromatic C<sub>q</sub>), 131.7 (aromatic or alkene CH), 127.7 (aromatic or alkene CH), 126.9 (aromatic or alkene CH), 125.4 (aromatic or alkene CH), 124.3 (aromatic or alkene CH), 123.2 (aromatic or alkene CH), 78.7 (CH-OH), 67.1 (CH<sub>2</sub>-O), 54.4 (ring C<sub>q</sub>), 41.5 (ring junction CH), 25.9 (Si-C<sub>q</sub>-(CH<sub>3</sub>)<sub>3</sub>), 22.4 (CH<sub>2</sub>-CH<sub>2</sub>-CH), 21.9 (CH<sub>2</sub>-CH<sub>2</sub>-CH), 18.3 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub>), -5.4 (Si-CH<sub>3</sub>), -5.4 (Si-CH<sub>3</sub>).

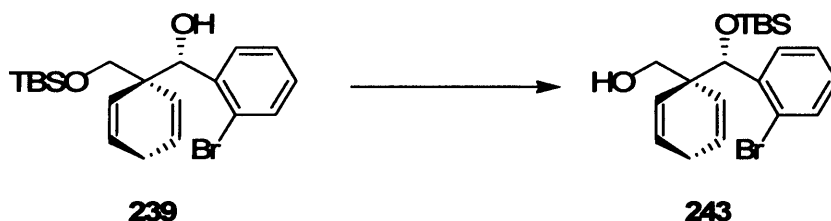
**Acetic acid 1-(1-acetoxymethyl-cyclohexa-2,5-dienyl)-1-(2-bromophenyl)-methyl ester (242)**



Acetic anhydride (27 mg, 0.26 mmol, 1.1 equiv.) was added to a solution of silyl ether **239** (100 mg, 0.24 mmol, 1.0 equiv.) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 ml). Triethylamine (49 mg, 0.49 mmol, 2.0 equiv.) was added followed by DMAP (one crystal). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 24 h then quenched with aqueous 2 M HCl solution (5 ml). The organic material was

extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 ml). The combined extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford a yellow oil. Purification by flash column chromatography (eluting with Et<sub>2</sub>O-hexane 2:8) afforded the *title compound* (6.0 mg, 5 %) as a colourless oil;  $\delta_{\text{H}}$  (250 MHz; CDCl<sub>3</sub>) 7.41 (1 H, dd, *J* 7.9, 1.4, aromatic CH), 7.26 (1 H, dd, *J* 7.8, 1.9, aromatic CH), 7.13 (1 H, app. td, *J* 7.6, 1.2, aromatic CH), 7.02 (1 H, app. td, *J* 7.9, 1.9, aromatic CH), 6.30 (1 H, s, CH-OAc), 5.96 – 5.87 (1 H, m, one of CH=CH-CH<sub>2</sub>), 5.77 (1 H, app. dq, *J* 9.7, 1.9, one of CH=CH-CH<sub>2</sub>), 5.72 – 5.56 (2 H, m, one of CH=CH-CH<sub>2</sub> and one of CH=CH-CH<sub>2</sub>), 4.22 (1 H, d, *J* 10.8, one of CH<sub>2</sub>-O), 3.93 (1 H, d, *J* 10.8, one of CH<sub>2</sub>-O), 2.46 – 2.32 (1 H, m, one of ring CH<sub>2</sub>), 2.10 – 2.03 (1 H, m, one of ring CH<sub>2</sub>), 2.02 (3 H, s, one of O-CH<sub>3</sub>), 1.98 (3 H, s, one of O-CH<sub>3</sub>).

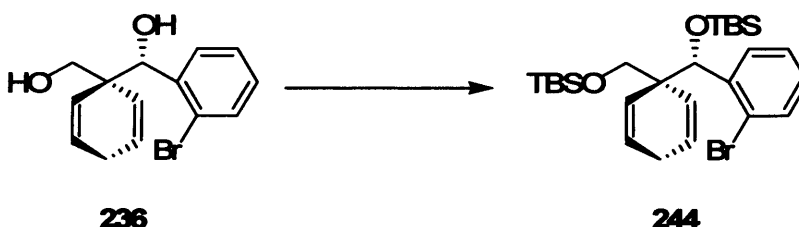
**{1-[(2-Bromophenyl)-(tert-butyldimethylsilyloxy)-methyl]-cyclohexa-2,5-dienyl}-methanol (243)**



A solution of silyl ether **239** (100 mg, 0.24 mmol, 1.0 equiv.) in dry THF (5 ml) was added carefully to a suspension of sodium hydride (60 % dispersion, 14.7 mg, 0.37 mmol, 1.5 equiv.) in dry THF (5 ml). Benzyl bromide (0.03 ml, 0.24 mmol, 1.0 equiv.) was added and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 24 hours. Saturated ammonium chloride solution (10 ml) was added and the organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 ml). The combined extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford a yellow oil. Purification by flash column chromatography (eluting with Et<sub>2</sub>O-hexane 0.5:9.5) afforded the *title compound* (17 mg, 17 %) as a colourless oil;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.40 (1 H, dd, *J* 7.9, 1.8, aromatic CH), 7.36 (1 H, dd, *J* 8.0, 1.0, aromatic CH), 7.15 (1 H, app. td, *J* 7.9, 0.9, aromatic CH), 6.99 (1 H, app. td, *J* 7.7, 1.6, aromatic CH), 5.90 (2 H, app. dt, *J* 10.6, 1.9, 2 × CH=CH-CH<sub>2</sub>), 5.68 – 5.61 (2 H, m, 2 × CH=CH-CH<sub>2</sub>), 5.10 (1 H, s, CH-O-Si), 3.70 (1 H, d, *J* 10.3, one of

CH<sub>2</sub>-OH), 3.58 (1 H, d, *J* 10.3, one of CH<sub>2</sub>-OH), 2.47 – 2.34 (1 H, m, one of ring CH<sub>2</sub>), 2.17 – 2.05 (1 H, m, one of ring CH<sub>2</sub>), 0.79 (9 H, s, Si-C(CH<sub>3</sub>)<sub>3</sub>), 0.00 (3 H, s, Si-CH<sub>3</sub>), -0.41 (3 H, s, Si-CH<sub>3</sub>);  $\delta_c$  (100 MHz; CDCl<sub>3</sub>) 140.7 (aromatic C<sub>q</sub>), 131.8 (aromatic or alkene CH), 130.8 (aromatic or alkene CH), 129.1 (aromatic or alkene CH), 128.6 (aromatic or alkene CH), 128.1 (aromatic or alkene CH), 127.7 (aromatic or alkene CH), 126.5 (aromatic or alkene CH), 125.7 (aromatic or alkene CH), 123.6 (C<sub>q</sub>-Br), 76.5 (CH-O-Si), 68.5 (CH<sub>2</sub>-OH), 49.5 (ring C<sub>q</sub>), 26.6 (ring CH<sub>2</sub>), 25.8 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub>), 18.0 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub>), -4.8 (Si-CH<sub>3</sub>), -5.3 (Si-CH<sub>3</sub>).

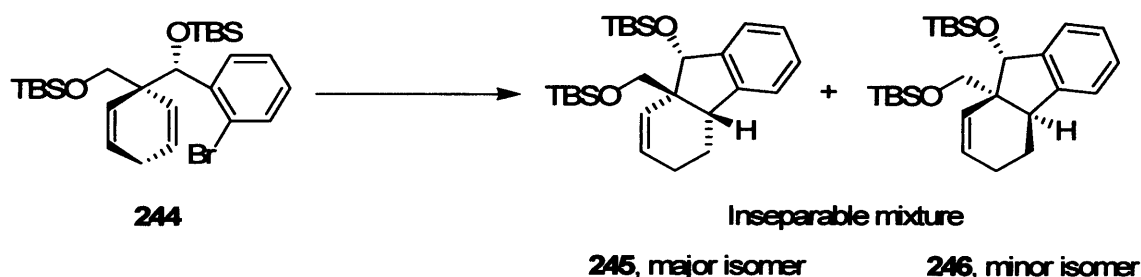
**1-Bromo-2-((*tert*-butyldimethylsilanyloxy)-[1-(*tert*-butyldimethylsilanyloxymethyl)-cyclohexa-2,5-dienyl]-methyl)-benzene (244)**



*t*-Butyldimethylsilyl trifluoromethane sulfonate (1.3 ml, 5.7 mmol, 2.2 equiv.) was added to a cooled solution (0 °C) of diol **236** (760 mg, 2.6 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (25 ml). 2,6-Lutidine (1.8 ml, 15.5 mmol, 6.0 equiv.) was added and the resulting mixture was stirred at this temperature under a nitrogen atmosphere for two hours then at room temperature for 24 hours. Aqueous 2 M HCl solution (15 ml) was added and the organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 25 ml). The combined extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford a brown oil. Purification by flash chromatography (eluting with ethyl acetate-hexane 0.2:9.8) afforded the *title compound* (472 mg, 35 %) as a colourless solid, m.p. 43 – 44 °C ;  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3030, 2954, 2885, 2857, 1470, 1252, 1101, 1070, 873, 838, 776;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 7.38 (1 H, dd, *J* 7.8, 1.7, aromatic CH), 7.33 (1 H, dd, *J* 8.0, 1.1, aromatic CH), 7.09 (1 H, app. td, *J* 7.6, 1.0, aromatic CH), 6.95 (1 H, app. td, *J* 7.7, 1.7, aromatic CH), 5.83 (1 H, app. dq, *J* 10.4, 1.9, one of CH=CH-CH<sub>2</sub>), 5.80 – 5.75 (1 H, m, one of CH=CH-CH<sub>2</sub>), 5.70 (1 H, app. dq, *J* 10.4, 1.8, one of CH=CH-CH<sub>2</sub>), 5.51 (1 H, s, CH-Ar), 5.40 – 5.34 (1 H, m, one of CH=CH-CH<sub>2</sub>), 3.84 (1 H, d, *J* 9.1, one of CH<sub>2</sub>-O), 3.29 (1 H, d, *J* 9.1, one of CH<sub>2</sub>-O), 2.31 (1 H,

app. dtt,  $J$  22.6, 3.5, 1.8, one of ring  $\text{CH}_2$ ), 1.91 (1 H, app. doubled quintet,  $J$  22.6, 2.5, 1.8, one of ring  $\text{CH}_2$ , one of ring  $\text{CH}_2$ ), 0.90 (9 H, s, one of  $\text{Si}-\text{C}_q(\text{CH}_3)_3$ ), 0.80 (9 H, s, one of  $\text{Si}-\text{C}_q(\text{CH}_3)_3$ ), 0.03 (3 H, s, one of  $\text{CH}-\text{O}-\text{Si}-\text{CH}_3$ ), 0.00 (6 H, s,  $\text{CH}_2-\text{O}-\text{Si}(\text{CH}_3)_2$ ), -0.41 (3 H, s, one of  $\text{CH}-\text{O}-\text{Si}-\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 141.9 (aromatic  $\text{C}_q$ ), 131.5 (aromatic or alkene CH), 130.9 (aromatic or alkene CH), 128.0 (aromatic or alkene CH), 127.9 (aromatic or alkene CH), 127.6 (aromatic or alkene CH), 126.0 (aromatic or alkene CH), 125.6 (aromatic or alkene CH), 124.5 (aromatic or alkene CH), 123.8 ( $\text{C}_q-\text{Br}$ ), 73.0 ( $\text{CH}-\text{O}$ ), 67.4 ( $\text{CH}_2-\text{O}$ ), 46.2 (ring  $\text{C}_q$ ), 26.8 (ring  $\text{CH}_2$ ), 26.0 ( $\text{Si}-\text{C}_q-(\text{CH}_3)_3$ ), 25.8 ( $\text{Si}-\text{C}_q-(\text{CH}_3)_3$ ), 18.3 ( $\text{Si}-\text{C}_q-(\text{CH}_3)_3$ ), 18.1 ( $\text{Si}-\text{C}_q-(\text{CH}_3)_3$ ), -4.7 ( $\text{Si}-\text{CH}_3$ ), -5.1 ( $\text{Si}-\text{CH}_3$ ), -5.2 ( $\text{Si}-\text{CH}_3$ ), -5.4 ( $\text{Si}-\text{CH}_3$ ).

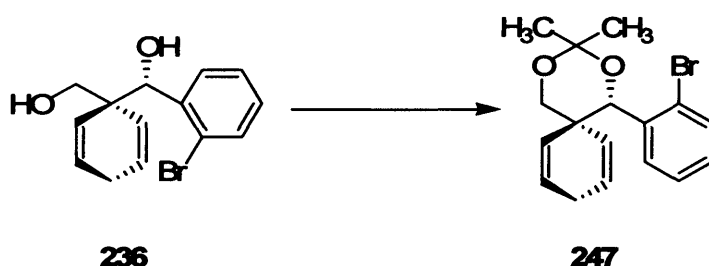
**(4aSR,9RS,9aSR)-9-(tert-Butyl-dimethyl-silanyloxy)-9a-(tert-butyl-dimethyl-silanoxyethyl)-4,4a,9,9a-tetrahydro-3H-fluorene (245) (major isomer) and (4aRS,9RS,9aRS)-9-(tert-Butyl-dimethyl-silanyloxy)-9a-(tert-butyl-dimethyl-silanoxyethyl)-4,4a,9,9a-tetrahydro-3H-fluorene (246) (minor isomer)**



AIBN (17 mg, 0.104 mmol, 0.38 equiv.) was added to a solution of bromide **244** (139 mg, 0.27 mmol, 1.0 equiv.) in dry benzene (15 ml). After heating the mixture to reflux, tributyltin hydride (0.07 ml, 0.27 mmol, 1.0 equiv.) was added and the resulting mixture was refluxed for 5 hours under a nitrogen atmosphere. The solvent was removed on a rotary evaporator to afford the crude product as a yellow oil containing two isomers (major:minor ratio 10: 1.0). Purification by flash column chromatography (eluting with neat hexane) afforded a mixture of the two isomers containing mainly the major isomer (61 mg, 52 %) as a very viscous colourless oil which solidified into a colourless solid, m.p. 59 – 60 °C (Found:  $(\text{M}+\text{NH}_4)^+$ , 462.3213.  $\text{C}_{26}\text{H}_{48}\text{O}_2\text{NSi}_2$  requires  $\text{M}$ , 462.3218);  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3027, 2955, 2881, 2857, 1472, 1361, 1256, 1110, 1087, 1065, 1006, 899, 871, 835;  $\delta_{\text{H}}$  (400 MHz;

CDCl<sub>3</sub>) 7.20 – 7.10 (4 H, m, aromatic CH), 5.56 – 5.61 (1 H, m, CH=CH-CH<sub>2</sub>), 5.51 (1 H, d, *J* 10.3, CH=CH-CH<sub>2</sub>), 5.37 (1 H, s, CH-Ar), 3.58 (1 H, d, *J* 10.5 one of CH<sub>2</sub>-O), 3.43 (1 H, d, *J* 10.5 one of CH<sub>2</sub>-O), 3.22 (1 H, app. t, *J* 3.9, ring junction CH), 2.10 – 2.04 (1 H, m, one of =CH-CH<sub>2</sub>), 1.85 – 1.66 (3 H, m, one of =CH-CH<sub>2</sub> and 2 × CH=CH-CH<sub>2</sub>), 0.92 (9 H, s, 3 × CH<sub>3</sub>), 0.82 (9 H, s, 3 × CH<sub>3</sub>), 0.17 (3 H, s, one of O-Si-CH<sub>3</sub>), 0.13 (3 H, s, one of O-Si-CH<sub>3</sub>), 0.01 (3 H, s, one of O-Si-CH<sub>3</sub>), 0.00 (3 H, s, one of O-Si-CH<sub>3</sub>); δ<sub>C</sub> (100 MHz; CDCl<sub>3</sub>) 145.3 (aromatic C<sub>q</sub>), 142.3 (aromatic C<sub>q</sub>), 130.1 (aromatic or alkene CH), 126.9 (aromatic or alkene CH), 126.6 (aromatic or alkene CH), 126.2 (aromatic or alkene CH), 123.9 (aromatic or alkene CH), 122.9 (aromatic or alkene CH), 76.2 (CH-O), 63.0 (CH<sub>2</sub>-O), 55.6 (ring junction C<sub>q</sub>), 39.3 (ring junction CH), 26.0 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub>), 25.9 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub>), 21.5 (CH<sub>2</sub>-CH<sub>2</sub>-CH), 19.8 (CH<sub>2</sub>-CH<sub>2</sub>-CH), 18.4 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub>), 18.3 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub>), -4.0 (Si-CH<sub>3</sub>), -4.5 (Si-CH<sub>3</sub>), -5.3 (Si-CH<sub>3</sub>), -5.5 (Si-CH<sub>3</sub>); *m/z* (APCI) 444 (M<sup>+</sup>, 10 %), 443 (100).

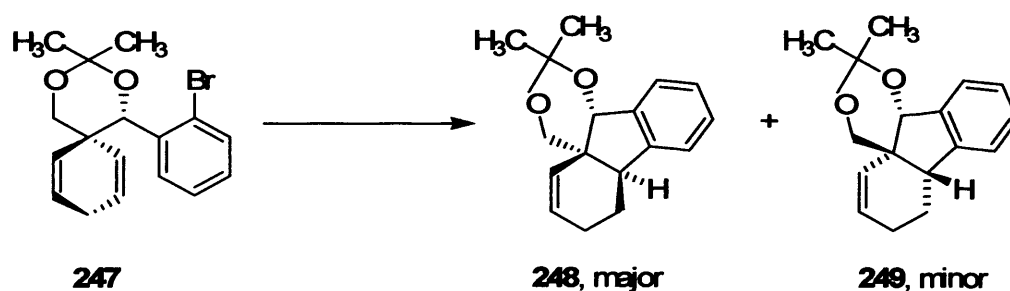
**1-(2-Bromophenyl)-3,3-dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (247)**



2,2-Dimethoxypropane (7.5 ml, 61.0 mmol, 5.04 equiv.) was added to a solution of diol **236** (3.56 g, 12.1 mmol) and camphorsulfonic acid (112 mg, 0.48 mmol, 0.04 equiv.) in dry acetone (180 ml). The resulting mixture was stirred under reflux under a nitrogen atmosphere for 48 h then most of the solvent was evaporated on the rotary evaporator. The remaining solution was neutralised with saturated NaHCO<sub>3</sub> solution and H<sub>2</sub>O (50 ml) was added. The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 50 ml). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford the *title compound* (3.1 g, 91 %) as an essentially-pure pale yellow waxy solid, m.p. 68 - 69 °C (Found: (M+NH<sub>4</sub>)<sup>+</sup>, 352.0903. C<sub>17</sub>H<sub>23</sub>NO<sub>2</sub><sup>79</sup>Br requires M, 352.0907); ν<sub>max</sub> (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3024, 2990, 2854, 2815, 1472, 1439, 1380, 1282, 1244, 1198, 1165, 1120, 1063, 1030, 940, 889, 746; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 7.40 (1 H, dd, *J* 7.9, 1.8, aromatic CH), 7.37 (1 H, dd, *J* 8.0, 1.3,

aromatic CH), 7.17 (1 H, app. td,  $J$  7.7, 1.3, aromatic CH), 7.00 (1 H, app. td,  $J$  7.7, 1.8, aromatic CH), 6.25 (1 H, app. dq,  $J$  10.4, 2.0, one of  $\text{CH}=\text{CH}-\text{CH}_2$ ), 5.73 – 5.67 (1 H, m, one of  $\text{CH}=\text{CH}-\text{CH}_2$ ), 5.65 – 5.60 (1 H, m, one of  $\text{CH}=\text{CH}-\text{CH}_2$ ), 5.52 (1 H, app. dq,  $J$  10.2, 1.9, one of  $\text{CH}=\text{CH}-\text{CH}_2$ ), 5.37 (1 H, s,  $\text{CH}-\text{Ar}$ ), 3.98 (1 H, d,  $J$  11.3, one of  $\text{O}-\text{CH}_2$ ), 3.57 (1 H, d,  $J$  11.3, one of  $\text{O}-\text{CH}_2$ ), 2.34 (1 H, app. dtt,  $J$  22.9, 3.7, 1.6, one of ring  $\text{CH}_2$ ), 1.90 (1 H, app. doubled quintet,  $J$  22.9, 2.6, one of ring  $\text{CH}_2$ ), 1.57 (3 H, s, one of  $\text{CH}_3$ ), 1.48 (3 H, s, one of  $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 137.6 (aromatic  $\text{C}_q$ ), 131.9 (alkene or aromatic CH), 131.1 (alkene or aromatic CH), 128.9 (alkene or aromatic CH), 128.3 (alkene or aromatic CH), 126.4 (alkene or aromatic CH), 126.2 (alkene or aromatic CH), 126.1 (alkene or aromatic CH), 125.6 (alkene or aromatic CH), 123.9 ( $\text{C}_q-\text{Br}$ ), 99.6 ( $\text{O}-\text{C}_q-\text{O}$ ), 76.3 ( $\text{O}-\text{CH}-\text{Ar}$ ), 70.3 ( $\text{O}-\text{CH}_2$ ), 42.4 (ring  $\text{C}_q$ ), 29.7 ( $\text{CH}_3$ ), 26.8 (ring  $\text{CH}_2$ ), 18.9 ( $\text{CH}_3$ );  $m/z$  (APCI) 337 ( $\text{MH}^+$  ( $^{81}\text{Br}$ ), 16 %), 335 ( $\text{MH}^+$  ( $^{79}\text{Br}$ ), 13 %), 279 (33), 277 (33), 261 (23), 259 (20), 185 (100), 180 (100), 143 (16), 137 (28).

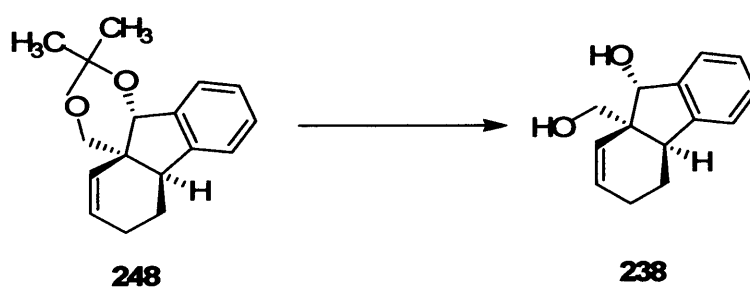
**((4*bRS*,8*aRS*,9*RS*)-9-*tert*-Butoxy-4*b*,5,6,9-tetrahydro-fluoren-8*a*-yl)-methanol (248) and ((4*bSR*,8*aSR*,9*RS*)-9-*tert*-Butoxy-4*b*,5,6,9-tetrahydro-fluoren-8*a*-yl)-methanol (249)**



AIBN (257 mg, 1.57 mmol, 1.1 equiv.) was added to a solution of bromide 247 (477 mg, 1.42 mmol, 1.0 equiv.) in dry benzene (20 ml). After heating the mixture to reflux, tributyltin hydride (0.38 ml, 1.42 mmol, 1.0 equiv.) was added dropwise over 10 minutes then the resulting mixture was refluxed for 5 hours under a nitrogen atmosphere. The solvent was removed on a rotary evaporator to afford the crude product as a yellow oil (mixture of two isomers, major:minor ratio 6:1). Purification by flash column chromatography over silica gel containing 10 % solid KF (eluting with ethyl acetate-hexane 0.5:9.5) afforded the major isomer 248 (282 mg, 77 %) as

a colourless solid, m.p. 83 – 85 °C;  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 2990, 2922, 2865, 1460, 1378, 1264, 1238, 1198, 1160, 1108, 1049, 1015, 897,  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.30 (1 H, d, *J* 7.3, aromatic CH), 7.26 – 7.12 (3 H, m, aromatic CH), 5.62 – 5.56 (1 H, m, CH=CH-CH<sub>2</sub>), 5.26 – 5.21 (1 H, m, CH=CH-CH<sub>2</sub>), 4.74 (1 H, s, O-CH-Ar), 3.87 (1 H, d, *J* 12.5, one of O-CH<sub>2</sub>), 3.76 (1 H, d, *J* 12.5, one of O-CH<sub>2</sub>), 3.67 (1 H, broad resonance, ring junction CH), 2.21 – 2.12 (1 H, m, one of =CH-CH<sub>2</sub>), 1.87 – 1.69 (3 H, m, one of =CH-CH<sub>2</sub> and =CH-CH<sub>2</sub>-CH<sub>2</sub>), 1.55 (3 H, s, one of CH<sub>3</sub>), 1.29 (3 H, s, one of CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 146.3 (aromatic C<sub>q</sub>), 142.2 (aromatic C<sub>q</sub>), 131.2 (alkene or aromatic CH), 128.4 (alkene or aromatic CH), 128.2 (alkene or aromatic CH), 126.9 (alkene or aromatic CH), 125.7 (alkene or aromatic CH), 123.8 (alkene or aromatic CH), 97.5 (O-C<sub>q</sub>-O), 78.6 (O-CH-Ar), 64.2 (O-CH<sub>2</sub>), 44.7 (ring C<sub>q</sub>), 41.8 (ring junction CH), 28.9 (CH<sub>3</sub>), 21.0 (=CH-CH<sub>2</sub>), 19.5 (=CH-CH<sub>2</sub>-CH<sub>2</sub> and CH<sub>3</sub>, two distinct peaks in DEPT spectrum).

**(4*aRS*,9*RS*,9*aRS*)-9*a*-Hydroxymethyl-4,4*a*,9,9*a*-tetrahydro-3*H*-fluoren-9-ol (238)**

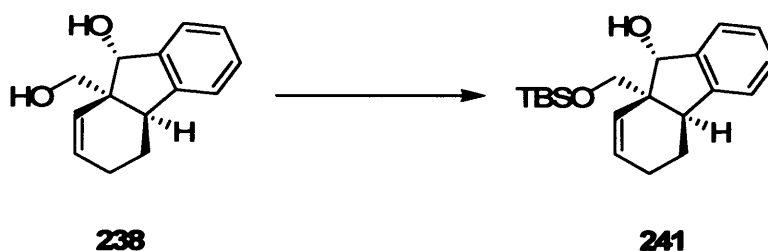


A mixture of acetic acid/water (1:1) (6 ml) was added to acetonide **248** (101 mg, 0.47 mmol). The resulting mixture was stirred at room temperature for 24 hours then water (25 ml) was added. The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to afford the *title compound* (61 mg, 72 %) as an essentially-pure pale yellow solid m.p. 73 - 74 °C;  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3376 (broad), 3016, 2923, 1479, 1460, 1428, 1069, 1008, 751;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.32 (1 H, d, *J* 7.1, aromatic CH), 7.27 – 7.14 (3 H, m, aromatic CH), 5.70 – 5.63 (1 H, m, CH=CH-CH<sub>2</sub>), 5.52 (1 H, d, *J* 10.3, CH=CH-CH<sub>2</sub>), 4.91 (1 H, s, CH-OH), 3.84 and 3.78 (2 H, AB quartet, *J* 11.3, CH<sub>2</sub>-OH), 3.48 (1 H, app. t, *J* 4.6, ring junction CH), 2.50 (2 H, broad resonance, 2 × OH), 2.00 – 1.67 (4 H, m, CH<sub>2</sub>-CH<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz;



CDCl<sub>3</sub>) 145.8 (aromatic C<sub>q</sub>), 143.5 (aromatic C<sub>q</sub>), 129.9 (aromatic or alkene CH), 129.0 (aromatic or alkene CH), 128.8 (aromatic or alkene CH), 127.2 (aromatic or alkene CH), 125.1 (aromatic or alkene CH), 124.0 (aromatic or alkene CH), 82.9 (CH-OH), 66.8 (CH<sub>2</sub>-OH), 51.7 (ring junction C<sub>q</sub>), 41.8 (ring junction CH), 22.4 (CH=CH-CH<sub>2</sub>), 21.5 (CH-CH<sub>2</sub>).

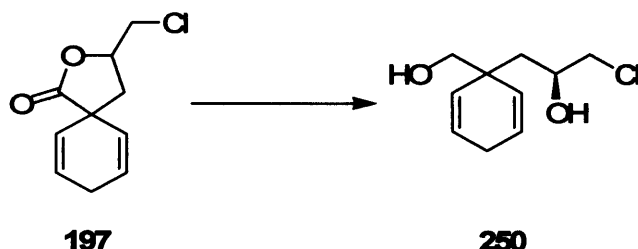
**(4a*RS*,9*RS*,9a*RS*)-9a-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4,4a,9,9a-tetrahydro-3*H*-fluoren-9-ol (241)**



*t*-Butyldimethylchlorosilane (429 mg, 2.85 mmol, 1.1 equiv.) was added to a solution of diol **238** (560 mg, 2.59 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 ml). Triethylamine (0.4 ml, 2.59 mmol, 1.1 equiv.) was added followed by DMAP (few crystals). The resulting mixture was stirred at room temperature under a nitrogen atmosphere for 48 h. then quenched with aqueous 2 M HCl solution (15 ml). The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 ml). The combined extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford a pale yellow oil. Purification by flash column chromatography (eluting with ethyl acetate-hexane 1.5:8.5) afforded the *title compound* (516 mg, 60 %) as a yellow oil;  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3450, 3021, 2926, 2857, 1742, 1462, 1390, 1255, 1084, 1006, 840, 776, 753;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.35 – 7.31 (1 H, m, aromatic CH), 7.19 – 7.09 (3 H, m, aromatic CH), 5.68 – 5.60 (1 H, m, CH=CH-CH<sub>2</sub>), 5.58 (1 H, d, *J* 10.3, CH=CH-CH<sub>2</sub>), 4.87 (1 H, s, CH-OH), 3.79 and 3.76 (2 H, AB quartet, *J* 10.0, CH<sub>2</sub>-O), 3.23 (1 H, app. t, *J* 5.2, ring junction CH), 1.90 – 1.71 (2 H, m, two of CH<sub>2</sub>-CH<sub>2</sub>), 1.65 – 1.51 (1 H, m, one of CH<sub>2</sub>-CH<sub>2</sub>), 1.32 – 1.41 (1 H, m, one of CH<sub>2</sub>-CH<sub>2</sub>), 0.77 (9 H, s, Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub>), 0.00 (3 H, s, Si-CH<sub>3</sub>), -0.16 (3 H, s, Si-CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 145.1 (aromatic C<sub>q</sub>), 144.2 (aromatic C<sub>q</sub>), 129.6 (aromatic or alkene CH), 128.9 (aromatic or alkene CH), 128.1 (aromatic or alkene CH), 127.0 (aromatic or alkene CH), 125.2 (aromatic or alkene CH), 123.5 (aromatic or alkene CH), 82.4 (CH-OH), 67.7 (CH<sub>2</sub>-OH), 51.1 (ring junction C<sub>q</sub>),

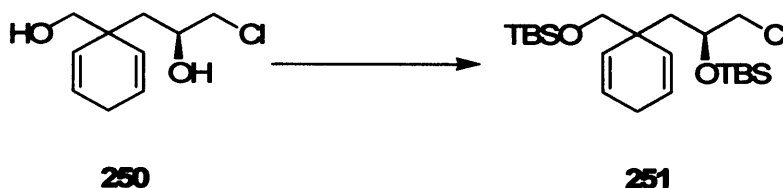
42.9 (ring junction CH), 25.8 (3 × CH<sub>3</sub>), 23.4 (CH=CH-CH<sub>2</sub>), 21.9 (CH-CH<sub>2</sub>), 18.1 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub>), -5.6 (Si-CH<sub>3</sub>), -5.9 (Si-CH<sub>3</sub>).

**1-Chloro-3-(1-hydroxymethyl-cyclohexa-2,5-dienyl)-propane-2-ol (250)**



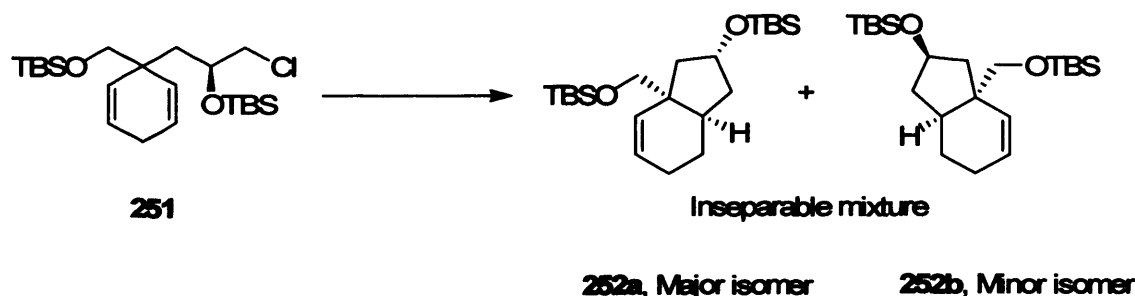
Sodium borohydride (61 mg, 1.6 mmol, 1.6 equiv.) was added to a solution of lactone **197** (200 g, 1.01 mmol) in ethanol (10 ml) at room temperature portionwise at such a rate to maintain the pH below 7. Then a further amount of NaBH<sub>4</sub> (72.4 mg, 1.9 equiv.) was added and stirring was continued for 24 h. Aqueous 2 M HCl solution (3 ml) was added and the excess ethanol was evaporated under reduced pressure. The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 ml). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated in *vacuo* to afford pale a yellow oil. Purification by flash chromatography (eluting with ethyl acetate-hexane in gradient mode 2:8 to 4:6) afforded the *title diol* (81 mg, 40 %) as a colourless oil;  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3386 (broad), 3115, 2925, 2865, 2815, 1634, 1423, 1373, 1258, 1146, 947, 878, 718;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 6.00 – 5.92 (2 H, m, 2 × CH=CH-CH<sub>2</sub>), 5.58 (1 H, app. dq, *J* 10.4, 2.0, one of CH=CH-CH<sub>2</sub>), 5.39 (1 H, app. dq, *J* 10.4, 2.1, one of CH=CH-CH<sub>2</sub>), 3.95 – 3.89 (1 H, m, O-CH), 3.50 (1 H, dd, *J* 11.1, 4.0, one of Cl-CH<sub>2</sub>), 3.41 (1 H, dd, *J* 11.1, 6.5, one of Cl-CH<sub>2</sub>), 3.33 (2 H, s, O-CH<sub>2</sub>), 2.83 – 2.57 (2 H, m, ring CH<sub>2</sub>), 1.58 (1 H, dd, *J* 14.3, 8.1, one of CH<sub>2</sub>-C<sub>q</sub>), 1.49 (1 H, dd, *J* 14.3, 3.4, one of CH<sub>2</sub>-C<sub>q</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 129.8 (alkene CH), 129.4 (alkene CH), 128.1 (alkene CH), 127.8 (alkene CH), 70.3 (Cl-CH<sub>2</sub>), 69.1 (O-CH), 50.3 (O-CH<sub>2</sub>), 41.9 (CH<sub>2</sub>-C<sub>q</sub>), 41.9 (ring C<sub>q</sub>), 26.5 (ring CH<sub>2</sub>).

**3-[(2-(*tert*-Butyldimethylsilyloxy)-3-chloropropyl]-3-(*tert*-butyldimethylsilyloxymethyl)-cyclohexa-1,4-diene (251)**



*t*-Butyldimethylsilyl trifluoromethane sulfonate (0.48 ml, 2.07 mmol, 4.4 equiv.) was added to a solution of diol **250** (95 mg, 0.47 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 ml). 2,6-Lutidine (0.33 ml, 2.8 mmol, 6.0 equiv.) was added and the resulting mixture was stirred at room temperature and under a nitrogen atmosphere for 3 days. Aqueous 2 M HCl solution (10 ml) was added and the organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 ml). The combined extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo* to afford brown oil. Purification by flash chromatography (eluting with ethyl acetate-hexane 0.5:9.5) afforded the *title compound* (185 mg, 91 %) as a colourless oil;  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 2956, 2885, 2856, 1472, 1256, 1094, 940, 837, 775;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 5.84 – 5.78 (2 H, m, 2 × CH=CH-CH<sub>2</sub>), 5.53 (1 H, app. dq, *J* 10.3, 2.0, one of CH=CH-CH<sub>2</sub>), 5.41 (1 H, app. dq, *J* 10.3, 2.1 one of CH=CH-CH<sub>2</sub>), 3.84 – 3.77 (1 H, m, CH-O), 3.59 (1 H, dd, *J* 11.1, 3.2, one of CH<sub>2</sub>-Cl), 3.38 (1 H, dd, *J* 11.1, 6.1, one of CH<sub>2</sub>-Cl), 3.29 (2 H, app. s., CH<sub>2</sub>-O), 2.66 – 2.61 (2 H, m, ring CH<sub>2</sub>), 1.79 (1 H, dd, *J* 14.4, 3.8, one of CH<sub>2</sub>-C<sub>q</sub>), 1.72 (1 H, dd, *J* 14.4, 8.1, one of CH<sub>2</sub>-C<sub>q</sub>), 0.88 (9 H, s, SiC<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub>), 0.86 (9 H, s, Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub>), 0.07 (3 H, s, one of CH-O-SiCH<sub>3</sub>), 0.05 (3 H, s, one of CH-O-SiCH<sub>3</sub>), 0.00 (6 H, s, CH<sub>2</sub>-O-Si(CH<sub>3</sub>)<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 130.6 (alkene CH), 130.1 (alkene CH), 125.8 (alkene CH), 125.3 (alkene CH), 71.7 (CH<sub>2</sub>-Cl), 70.8 (CH-O), 50.6 (CH<sub>2</sub>-O), 42.5 (CH<sub>2</sub>-C<sub>q</sub>), 41.1 (ring C<sub>q</sub>), 26.7 (ring CH<sub>2</sub>), 25.9 (2 × SiC(CH<sub>3</sub>)<sub>3</sub>), 18.3 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub>), 18.1 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub>), -4.3 (Si-CH<sub>3</sub>), -4.5 (Si-CH<sub>3</sub>), -5.4 (Si-CH<sub>3</sub>), -5.5 (Si-CH<sub>3</sub>).

**(2*RS*,3*aRS*,7*aRS*)-2-(*tert*-Butyldimethylsilanoxy)-7*a*-(*tert*-butyldimethylsilanoxymethyl)-2,3,3*a*,4,5,7*a*-hexahydro-1*H*-indene (252a) and (2*RS*,3*aSR*,7*aSR*)-2-(*tert*-Butyldimethylsilanoxy)-7*a*-(*tert*-butyldimethylsilanoxymethyl)-2,3,3*a*,4,5,7*a*-hexahydro-1*H*-indene (252b)**

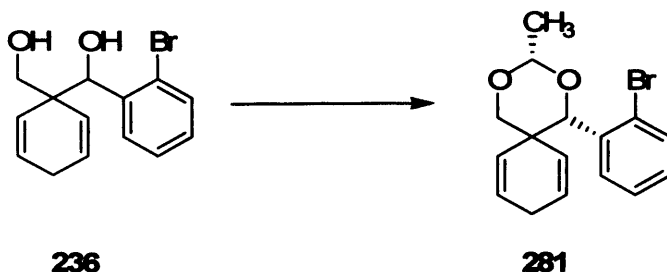


AIBN (85 mg, 0.52 mmol, 1.5 equiv.) was added to a solution of chloro silyl ether **251** (148 mg, 0.34 mmol, 1.0 equiv.) in dry benzene (15 ml). After heating the mixture to reflux, tributyltin hydride (0.14 ml, 0.52 mmol, 1.5 equiv.) was added and the resulting mixture was refluxed for 30 hours. The solvent was removed under reduced pressure to afford the crude product as a yellow oil (mixture of two isomers major:minor ratio 4.8: 1.0). Purification by flash column chromatography over silica gel containing KF 10 % w/w (eluting with ethyl acetate-hexane 0.6:9.4) afforded the *title compounds* as a mixture of the two diastereoisomers (63 mg, 46 %) as a pale yellow oil;  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  2928, 2856, 1464, 1255, 1094, 836, 774;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.69 – 5.60 (2 H, m,  $\text{CH}=\text{CH}-\text{CH}_2$ , of both major and minor isomers), 5.44 – 5.36 (2 H, m,  $\text{CH}=\text{CH}-\text{CH}_2$  of each isomer), 4.18 (1 H, app. quintet,  $J$  5.6, CH-O of major isomer), 4.16 – 4.08 (1 H, m, CH-O of minor isomer), 3.43 and 3.40 (2 H, AB quartet,  $J$  9.5,  $\text{CH}_2$ -O of major isomer), 3.26 – 3.23 (2 H, AB quartet,  $J$  9.8,  $\text{CH}_2$ -O of minor isomer), 2.24 (1 H, app. tt,  $J$  8.4, 4.1, ring junction CH of major isomer), 2.13 – 2.04 (1 H, m, ring junction CH of minor isomer), 2.01 – 1.78 (4 H, m,  $\text{CH}_2$  one of each isomer), 1.73 – 1.38 (12 H, m,  $3 \times \text{CH}_2$  of each isomer), 0.90 (9 H, s,  $3 \times \text{CH}_3$  of minor isomer), 0.87 (9 H, s,  $3 \times \text{CH}_3$  of minor isomer), 0.87 (9 H, s,  $3 \times \text{CH}_3$  of major isomer), 0.85 (9 H, s,  $3 \times \text{CH}_3$  of major isomer), 0.05 (3 H, s, one of  $\text{CH}_3$ -Si of minor isomer), 0.00 (18 H, s,  $4 \times \text{CH}_3$ -Si of major isomer and  $2 \times \text{CH}_3$ -Si of minor isomer), -0.05 (3 H, s, one of  $\text{CH}_3$ -Si of minor isomer);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 133.7 (alkene CH of major isomer), 133.3 (alkene CH of minor isomer), 126.5 (alkene CH of major isomer), 125.5 (alkene CH of minor), 72.3 (CH-O of major isomer), 72.0

(CH-O of minor isomer), 70.2 (CH<sub>2</sub>-O of major), 68.7 (CH<sub>2</sub>-O of minor isomer),  
 46.2 (ring junction C<sub>q</sub> of major isomer), 45.4 (ring junction C<sub>q</sub> of minor isomer), 45.1  
 (CH<sub>2</sub> of major isomer), 44.3 (CH<sub>2</sub> of minor isomer), 39.7 (CH<sub>2</sub> of minor isomer),  
 39.5 (CH<sub>2</sub> of major isomer), 36.3 (ring junction CH of major isomer), 35.5 (ring  
 junction CH of minor isomer), 25.9 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub> of both isomers), 25.8 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub>  
 of major isomer), 23.7 (CH<sub>2</sub> of major isomer), 22.8 (CH<sub>2</sub> of minor isomer), 21.2  
 (CH<sub>2</sub> of minor isomer), 20.8 (CH<sub>2</sub> of major isomer), 18.4 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub> of major  
 isomer), 18.3 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub> of minor isomer), 18.2 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub> of both isomers),  
 13.7 (Si-C<sub>q</sub>(CH<sub>3</sub>)<sub>3</sub> of minor isomer), -4.7 (CH<sub>3</sub>-Si), -4.7 (2 × CH<sub>3</sub>-Si), -5.4 (CH<sub>3</sub>-Si),  
 -5.4 (CH<sub>3</sub>-Si), -5.4 (CH<sub>3</sub>-Si), -5.5 (CH<sub>3</sub>-Si), -5.5 (CH<sub>3</sub>-Si).

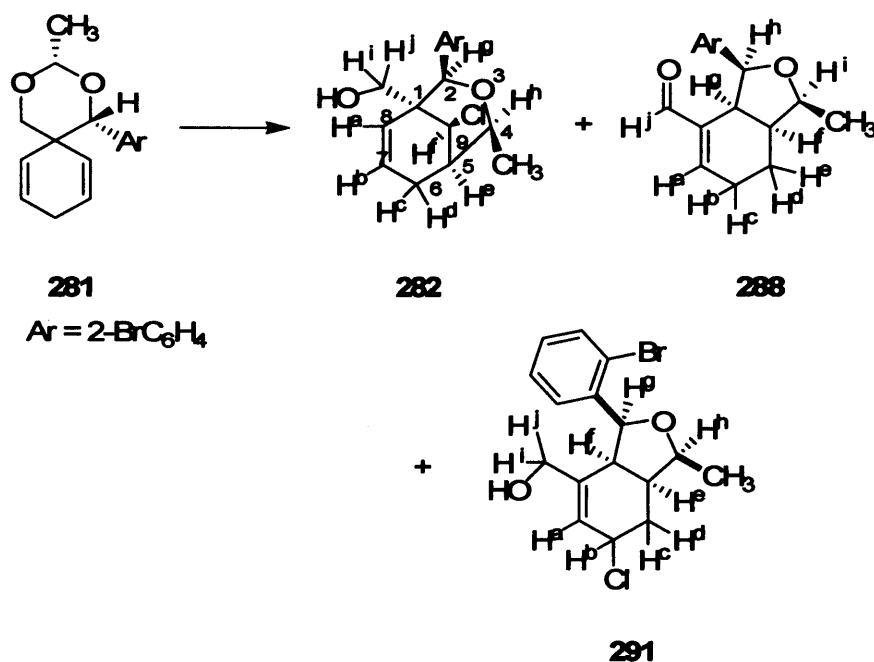
## 6.5. Experimental Data for Chapter 5

### (1*SR*,3*SR*)-1-(2-Bromophenyl)-3-methyl-2,4-dioxa-spiro[5.5]undeca-7,10-diene (281)



Acetaldehyde (3.3 g, 4.2 ml, 75.6 mmol, 7 equiv.) was added to a solution of diol **236** (3.2 g, 10.8 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (50 ml). Pyridinium *p*-toluenesulfonate (1.09 g, 4.3 mmol, 0.4 equiv.) was added and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 72 h. The mixture was poured into water (50 ml) and the organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 50 ml). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford compound **281** (3.1 g, 91 %) as an essentially-pure pale yellow oil which solidified upon cooling into an off-white solid, m.p. 52 - 54 °C (Found: (M+NH<sub>4</sub>)<sup>+</sup> 338.0753. C<sub>16</sub>H<sub>21</sub>NO<sub>2</sub><sup>79</sup>Br requires M, 338.0750);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3025, 2991, 2858, 2360, 1698, 1474, 1410, 1162, 1117, 1032, 911;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.37 (2 H, app. dd, *J* 7.9, 1.3, 2 × aromatic CH), 7.20 – 7.14 (1 H, m, aromatic CH), 7.01 (1 H, app. td, *J* 7.6, 1.8, aromatic CH), 6.21 (1 H, app. dq, *J* 10.3, 2.0, CH=CH-CH<sub>2</sub>), 5.74 – 5.68 (1 H, m, one of CH=CH-CH<sub>2</sub>), 5.65 – 5.59 (1 H, m, one of CH=CH-CH<sub>2</sub>), 5.48 (1 H, app. dq, *J* 10.1, 2.0, one of CH=CH-CH<sub>2</sub>), 5.08 (1 H, s, CH-Ar), 4.94 (1 H, q, *J* 5.0, O-CH-CH<sub>3</sub>), 3.81 and 3.76 (2 H, AB quartet, *J* 11.0, O-CH<sub>2</sub>), 2.34 (1 H, app. dtt, *J* 22.8, 3.7, 1.8, one of ring CH<sub>2</sub>), 1.90 (1 H, app. double quintet, *J* 22.8, 2.6, one of ring CH<sub>2</sub>), 1.38 (3 H, d, *J* 5.0, O-CH-CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 137.3 (aromatic C<sub>q</sub>), 131.9 (alkene or aromatic CH), 130.9 (alkene or aromatic CH), 128.9 (alkene or aromatic CH), 128.5 (alkene or aromatic CH), 126.4 (alkene or aromatic CH), 126.4 (alkene or aromatic CH), 126.3 (alkene or aromatic CH), 125.3 (alkene or aromatic CH), 123.6 (C<sub>q</sub>-Br), 100.2 (O-CH-O), 83.7 (O-CH-Ar), 76.5 (O-CH<sub>2</sub>), 42.1 (ring C<sub>q</sub>), 26.8 (ring CH<sub>2</sub>), 21.1 (CH<sub>3</sub>); *m/z* (APCI) 324 (MH<sup>+</sup> (<sup>81</sup>Br), 19 %), 323 (MH<sup>+</sup> (<sup>79</sup>Br), 100 %), 303 (26), 293 (19), 259 (14), 185 (14), 91 (14).

## Kinetic Prins cyclisation of acetaldehyde acetal **281**

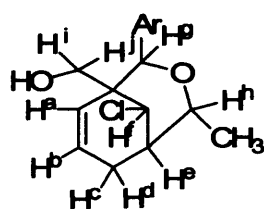


Titanium tetrachloride (2.0 mmol, 0.22 ml, 2 equiv.) was carefully added to a cooled (-78 °C) solution of acetaldehyde acetal **281** (1.0 mmol, 321 mg) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 ml) under a nitrogen atmosphere. The resulting mixture was stirred at this temperature for 4 h then carefully quenched with saturated NaHCO<sub>3</sub> solution (5 ml) followed by water (20 ml). The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml). The combined extracts were dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to afford a pale yellow residue. Purification by flash chromatography (eluted in gradient mode from EtOAc-hexane 1:9 to 3:7 to 4:6) afforded compound **282** as a pale yellow oil (12 mg, 3.4 %) and compound **288** as a colourless oil (18 mg, 5.6 %) respectively. While compound **291** was not isolated but its existence was evident from the data obtained from the crude reaction mixture.

**[(1*RS*,2*SR*,4*SR*,5*RS*,9*RS*)-2-(2-Bromophenyl)-9-chloro-4-methyl-3-oxa-bicyclo[3.3.1]non-7-en-1-yl]-methanol (**282**):** Pale yellow oil (12 mg, 3.4 %) (Found: MH<sup>+</sup>, 356.0167. C<sub>16</sub>H<sub>18</sub>O<sub>2</sub><sup>79</sup>Br<sup>35</sup>Cl requires M, 356.0173);  $\nu_{\text{max}}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3578, 3024, 2925, 1725, 1694, 1470, 1440, 1386, 1204, 1084;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.46 (1 H, dd, *J* 8.0, 1.2, aromatic CH), 7.40 (1 H, dd, *J* 7.8, 1.7, aromatic CH), 7.23 – 7.17 (1 H, m, aromatic CH), 7.08 (1 H, app. dt, *J* 1.7, 7.6, aromatic CH),

6.01 (1 H, app. dt,  $J$  9.9, 3.4,  $H^b$ ), 4.97 (1 H, s,  $H^g$ ), 4.81 (1 H, app. dq,  $J$  9.9, 1.9,  $H^a$ ), 4.68 (1H, dd,  $J$  3.3, 1.5,  $H^f$ ), 3.89 (1 H, app. dq,  $J$  1.7, 6.3,  $H^h$ ), 3.60 (1 H, d,  $J$  12.3,  $H^i$ ), 3.22 (1 H, d,  $J$  12.3,  $H^j$ ), 2.47 – 2.30 (2 H, m,  $H^c$  and  $H^d$ ), 2.12 – 2.06 (1 H, m, ring junction  $H^e$ ), 1.22 (3 H, d,  $J$  6.3,  $CH_3$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 137.5 (aromatic  $C_q$ ), 132.3 (alkene or aromatic CH), 131.5 (alkene or aromatic CH), 130.3 (alkene or aromatic CH), 129.7 (alkene or aromatic CH), 127.3 (alkene or aromatic CH), 123.5 ( $C_q$ -Br), 121.8 (alkene or aromatic CH), 80.7 (O-CH-Ar), 77.3 (O-CH-CH<sub>3</sub>), 63.2 (O-CH<sub>2</sub>), 63.1 (CH-Cl), 46.5 (ring  $C_q$ ), 41.1 (ring junction CH), 22.8 (ring CH<sub>2</sub>), 18.9 (CH<sub>3</sub>);  $m/z$  (APCI) 361 ( $MH^+$  ( $^{81}Br$   $^{37}Cl$ ) 13 %), 359 ( $MH^+$  ( $^{79}Br$   $^{37}Cl$ ) 48 %), 257 (44), 187 (65), 185 (75), 157 (25), 155 (65), 149 (29), 137 (100).

$^1H - ^1H$  COSY experiment showed the following correlations

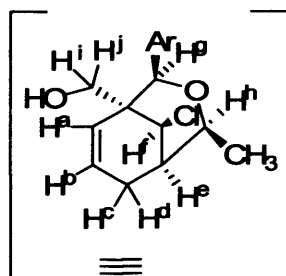


**282**

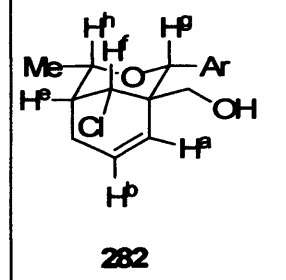
Ar = 2-BrC<sub>6</sub>H<sub>4</sub>

$H^a$ ,  $\delta$  = 4.81, showed a cross peak to  $H^b$ ,  $H^f$  &  $H^j$   
 $H^b$ ,  $\delta$  = 6.01, showed a cross peak to  $H^a$ ,  $H^f$  &  $H^j$   
 $H^c$  &  $H^d$ ,  $\delta$  = 2.47 - 2.30, showed a cross peak to  $H^e$ ,  $H^f$  &  $H^g$   
 $H^e$ ,  $\delta$  = 2.12 - 2.06, showed a cross peak to  $H^f$ ,  $H^d$  &  $H^j$   
 $H^f$ ,  $\delta$  = 4.68, showed a cross peak to  $H^e$   
 $H^g$ ,  $\delta$  = 5.16, it did not give any cross peaks  
 $H^h$ ,  $\delta$  = 4.68, showed a cross peak to  $CH_3$   
 $H^i$ ,  $\delta$  = 3.89, showed a cross peak to  $H^j$   
 $H^j$ ,  $\delta$  = 3.31, showed a cross peak to  $H^i$   
 $CH_3$ ,  $\delta$  = 1.22, showed a cross peak to  $H^h$

NOESY experiment showed the following correlations



≡



**282**

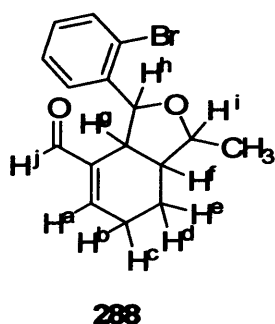
Ar = 2-BrC<sub>6</sub>H<sub>4</sub>

$H^a$ ,  $\delta$  = 4.81, showed a cross peak to  $H^b$  &  $H^j$   
 $H^b$ ,  $\delta$  = 6.01, showed a cross peak to  $H^a$ ,  $H^f$  &  $H^j$   
 $H^c$  &  $H^d$ ,  $\delta$  = 2.47 - 2.30, showed a cross peak to  $H^e$ ,  $H^f$  &  $CH_3$   
 $H^e$ ,  $\delta$  = 2.12 - 2.06, showed a cross peak to  $H^f$ ,  $H^d$ ,  $H^j$ ,  $H^h$  &  $CH_3$   
 $H^f$ ,  $\delta$  = 4.68, showed a cross peak to  $H^e$ ,  $H^g$  &  $H^h$   
 $H^g$ ,  $\delta$  = 5.16, showed a cross peak to  $H^f$  &  $H^h$   
 $H^h$ ,  $\delta$  = 4.68, showed a cross peak to  $H^g$ ,  $H^f$ ,  $H^e$  &  $CH_3$   
 $H^i$ ,  $\delta$  = 3.89, showed a cross peak to  $H^j$   
 $H^j$ ,  $\delta$  = 3.31, showed a cross peak to  $H^i$  &  $H^e$   
 $CH_3$ ,  $\delta$  = 1.22, showed a cross peak to  $H^h$ ,  $H^f$ ,  $H^d$  &  $H^e$



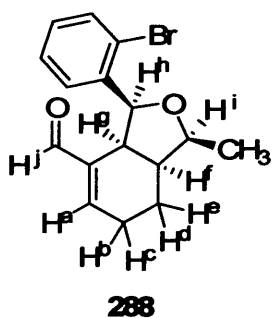
**(1*SR*,3*SR*,3*aSR*,7*aSR*)-3-(2-Bromophenyl)-1-methyl-1,3,3*a*,6,7,7*a*-hexahydro-isobenzofuran-4-carbaldehyde (288)**: colourless oil (18 mg, 5.6 %) (Found:  $(M+NH_4)^+$  338.0748.  $C_{16}H_{21}O_2N^{79}Br$  requires  $M$ , 338.0750);  $\nu_{max}$  ( $CH_2Cl_2$ )/ $cm^{-1}$  2935, 1685, 1641, 1472, 1441, 1392, 1212, 1162, 1089, 1018;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 8.79 (1 H, s,  $H^j$ ), 7.38 (1 H, app. dd,  $J$  8.7, 1.1, aromatic CH), 7.11 – 7.04 (2 H, m, 2  $\times$  aromatic CH), 6.94 (1 H, app. ddd,  $J$  8.1, 6.5, 2.5, aromatic CH), 6.75 (1 H, app. ddd,  $J$  5.0, 3.3, 1.0,  $H^a$ ), 5.54 (1 H, d,  $J$  9.4,  $H^h$ ), 4.07 (1 H, app. dq,  $J$  5.1, 6.5,  $H^i$ ), 3.56 (1 H, m, ring junction  $H^b$ ), 2.45 (1 H, app. dq,  $J$  19.1, 4.8,  $H^p$ ), 2.32 – 2.24 (1 H, m,  $H^f$ ), 2.24 – 2.13 (1 H, m,  $H^c$ ), 1.80 – 1.63 (2 H, m,  $H^d$  and  $H^e$ ), 1.31 (3 H, d,  $J$  6.5,  $CH_3$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 192.2 (O=CH), 151.0 (alkene CH), 141.0 ( $C_q=CH$ ), 137.6 (aromatic  $C_q$ ), 132.6 (aromatic CH), 130.3 (aromatic CH), 128.8 (aromatic CH), 126.5 (aromatic CH), 125.1 ( $C_q-Br$ ), 81.4 (O-CH-Ar), 77.1 (O-CH-CH<sub>3</sub>), 39.9 (Ar-CH-CH), 39.5 (CH<sub>3</sub>-CH-CH), 24.7 (ring =CH-CH<sub>2</sub>-CH<sub>2</sub>), 20.2 (=CH-CH<sub>2</sub>-CH<sub>2</sub>), 14.8 (CH<sub>3</sub>);  $m/z$  (APCI) 361 ( $M^+$  ( $^{81}Br$ ), 89 %), 321 ( $M^+$  ( $^{79}Br$ ), 100 %), 305 (24), 303 (27), 279 (40), 277 (27), 243 (16), 229 (11), 185 (18).

$^1H - ^1H$  COSY experiment showed the following correlations



$H^a$ ,  $\delta$  = 6.75, showed a cross peak to  $H^b$ ,  $H^f$  &  $H^p$   
 $H^b$ ,  $\delta$  = 2.45, showed a cross peak to  $H^a$ ,  $H^f$ ,  $H^d$  &  $H^p$   
 $H^c$ ,  $\delta$  = 2.24 – 2.13, showed a cross peak to  $H^a$ ,  $H^b$ ,  $H^d$  &  $H^p$   
 $H^d$  &  $H^e$ ,  $\delta$  = 1.80 – 1.63, showed a cross peak to  $H^b$ ,  $H^f$  &  $H^i$   
 $H^f$ ,  $\delta$  = 2.32 – 2.24, showed a cross peak to  $H^b$ ,  $H^i$ ,  $H^d$  &  $H^p$   
 $H^p$ ,  $\delta$  = 3.60 – 3.53, showed a cross peak to  $H^h$ ,  $H^f$  &  $H^i$   
 $H^h$ ,  $\delta$  = 5.54, showed a cross peak to  $H^p$   
 $H^i$ ,  $\delta$  = 4.07, showed a cross peak to  $H^f$  &  $CH_3$   
 $CH_3$ ,  $\delta$  = 1.31, showed a cross peak to  $H^i$

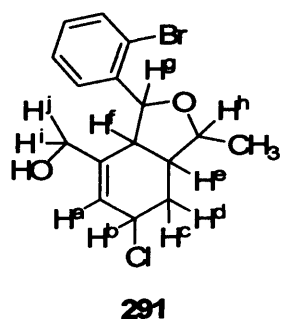
NOESY experiment showed the following correlations



$H^a$ ,  $\delta$  = 6.75, showed a cross peak to  $H^j$ ,  $H^b$  &  $H^f$   
 $H^b$ ,  $\delta$  = 2.45, showed a cross peak to  $H^a$ ,  $H^f$ ,  $H^d$  &  $H^p$   
 $H^c$ ,  $\delta$  = 2.24 – 2.13, showed a cross peak to  $H^a$ ,  $H^b$ ,  $H^d$  &  $H^p$   
 $H^d$  &  $H^e$ ,  $\delta$  = 1.80 – 1.63, showed a cross peak to  $H^b$ ,  $H^f$ ,  $H^i$ , two of aromatic H at  $\delta$  = 7.11 – 7.04 &  $CH_3$   
 $H^f$ ,  $\delta$  = 2.32 – 2.24, showed a cross peak to  $H^b$ ,  $H^i$ ,  $H^d$  &  $H^p$   
 $H^p$ ,  $\delta$  = 3.60 – 3.53, showed a cross peak to  $H^h$ ,  $H^f$  &  $H^i$   
 $H^h$ ,  $\delta$  = 5.54, showed a cross peak to  $H^p$  &  $H^i$   
 $H^i$ ,  $\delta$  = 4.07, showed a cross peak to  $H^f$ ,  $H^h$ ,  $H^p$  &  $CH_3$   
 $H^j$ ,  $\delta$  = 8.79, showed a cross peak to  $H^a$   
 $CH_3$ ,  $\delta$  = 1.31, showed a cross peak to  $H^i$ ,  $H^d$  &  $H^p$

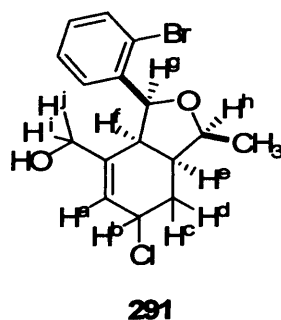
**[(1*SR*,3*SR*,3*aSR*,7*aSR*)-3-(2-Bromophenyl)-6-chloro-1-methyl-1,3,3*a*,6,7,7*a*-hexahydro-isobenzofuran-4-yl]-methanol (291):** This compound was not isolated pure. These data are obtained from the crude reaction mixture under the above conditions.  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.44 (1 H, d,  $J$  8.2, aromatic CH), 7.22 – 7.17 (1 H, m, aromatic CH), 7.10 – 7.02 (2 H, m, 2  $\times$  aromatic CH), 5.84 (1 H, d,  $J$  5.0,  $\text{H}^{\text{a}}$ ), 5.41 (1 H, d,  $J$  9.9,  $\text{H}^{\text{b}}$ ), 4.72 – 4.64 (1 H, m,  $\text{H}^{\text{b}}$ ), 4.10 (1H, app. dq,  $J$  4.8, 6.3,  $\text{H}^{\text{h}}$ ), 3.48 (1 H, d,  $J$  14.4,  $\text{H}^{\text{i}}$ ), 3.35 – 3.28 (2 H, m,  $\text{H}^{\text{j}}$  and  $\text{H}^{\text{f}}$ ), 2.70 – 2.61 (1 H, m,  $\text{H}^{\text{e}}$ ), 2.15 – 2.20 (2 H, m,  $\text{H}^{\text{c}}$  and  $\text{H}^{\text{d}}$ ), 1.30 (3 H, d,  $J$  6.3,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 140.9 ( $\text{C}_{\text{q}}=\text{CH}$ ), 138.0 (aromatic  $\text{C}_{\text{q}}$ ), 132.5 (aromatic or alkene CH), 129.8 (aromatic or alkene CH), 129.4 (aromatic or alkene CH), 127.6 (aromatic or alkene CH), 125.0 (aromatic or alkene CH), 124.0 ( $\text{C}_{\text{q}}-\text{Br}$ ), 81.1 ( $\text{O}-\text{CH}-\text{Ar}$ ), 76.9 ( $\text{O}-\text{CH}-\text{CH}_3$ ), 64.6 ( $\text{O}-\text{CH}_2$ ), 53.9 ( $\text{CH}-\text{Cl}$ ), 43.3 ( $\text{CH}-\text{C}=\text{CH}$ ), 36.9 ( $\text{CH}-\text{CH}-\text{CH}_3$ ), 29.9 (ring  $\text{CH}_2$ ), 14.8 ( $\text{CH}_3$ ).

$^1\text{H} - ^1\text{H}$  COSY experiment showed the following correlations



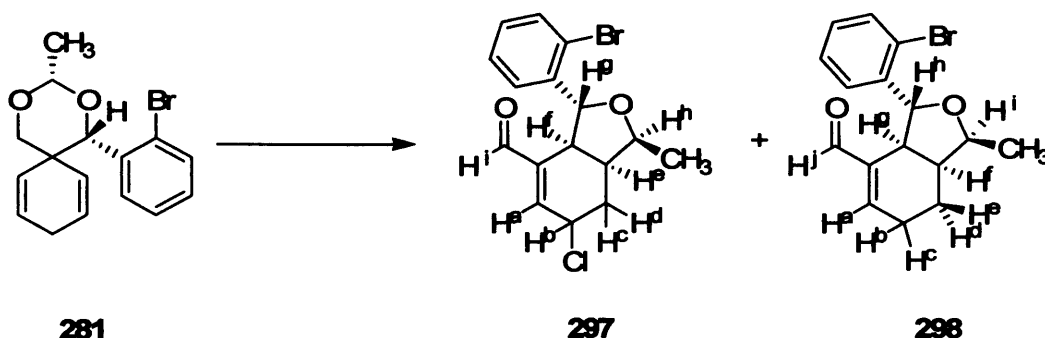
$\text{H}^{\text{a}}$ ,  $\delta = 5.84$ , showed a cross peak to  $\text{H}^{\text{b}}$  &  $\text{H}^{\text{f}}$   
 $\text{H}^{\text{b}}$ ,  $\delta = 4.72 - 4.64$ , showed a cross peak to  $\text{H}^{\text{a}}$ ,  $\text{H}^{\text{f}}$  &  $\text{H}^{\text{d}}$   
 $\text{H}^{\text{f}}$  &  $\text{H}^{\text{d}}$ ,  $\delta = 2.15 - 2.20$ , showed a cross peak to  $\text{H}^{\text{a}}$  &  $\text{H}^{\text{e}}$   
 $\text{H}^{\text{e}}$ ,  $\delta = 2.70 - 2.61$  showed a cross peak to  $\text{H}^{\text{f}}$ ,  $\text{H}^{\text{d}}$ ,  $\text{H}^{\text{f}}$  &  $\text{H}^{\text{h}}$   
 $\text{H}^{\text{b}}$ ,  $\delta = 5.41$ , showed a cross peak to  $\text{H}^{\text{f}}$   
 $\text{H}^{\text{h}}$ ,  $\delta = 4.10$ , showed a cross peak to  $\text{H}^{\text{a}}$  &  $\text{CH}_3$   
 $\text{H}^{\text{i}}$ ,  $\delta = 3.48$ , showed a cross peak to  $\text{H}^{\text{j}}$   
 $\text{H}^{\text{j}}$  &  $\text{H}^{\text{f}}$ ,  $\delta = 3.35 - 3.28$ , showed a cross peak to  $\text{H}^{\text{i}}$ ,  $\text{H}^{\text{a}}$ ,  $\text{H}^{\text{e}}$  &  $\text{H}^{\text{d}}$   
 $\text{CH}_3$ ,  $\delta = 1.30$ , showed a cross peak to  $\text{H}^{\text{h}}$

NOESY experiment showed the following correlations



$\text{H}^{\text{a}}$ ,  $\delta = 5.84$ , showed a cross peak to  $\text{H}^{\text{b}}$   
 $\text{H}^{\text{b}}$ ,  $\delta = 4.72 - 4.64$ , showed a cross peak to  $\text{H}^{\text{a}}$ ,  $\text{H}^{\text{f}}$  &  $\text{H}^{\text{d}}$   
 $\text{H}^{\text{f}}$  &  $\text{H}^{\text{d}}$ ,  $\delta = 2.15 - 2.20$ , showed a cross peak to  $\text{H}^{\text{a}}$ ,  $\text{H}^{\text{e}}$  &  $\text{CH}_3$   
 $\text{H}^{\text{e}}$ ,  $\delta = 2.70 - 2.61$ , showed a cross peak to  $\text{H}^{\text{f}}$ ,  $\text{H}^{\text{d}}$ ,  $\text{H}^{\text{f}}$  &  $\text{H}^{\text{h}}$   
 $\text{H}^{\text{b}}$ ,  $\delta = 5.41$ , showed a cross peak to  $\text{H}^{\text{f}}$  &  $\text{H}^{\text{e}}$   
 $\text{H}^{\text{h}}$ ,  $\delta = 4.10$ , showed a cross peak to  $\text{H}^{\text{a}}$ ,  $\text{H}^{\text{f}}$ ,  $\text{H}^{\text{e}}$  &  $\text{CH}_3$   
 $\text{H}^{\text{i}}$ ,  $\delta = 3.48$ , showed a cross peak to  $\text{H}^{\text{j}}$   
 $\text{H}^{\text{j}}$  &  $\text{H}^{\text{f}}$ ,  $\delta = 3.35 - 3.28$ , showed a cross peak to  $\text{H}^{\text{a}}$ ,  $\text{H}^{\text{h}}$ ,  $\text{H}^{\text{i}}$  &  $\text{H}^{\text{e}}$   
 $\text{CH}_3$ ,  $\delta = 1.30$ , showed a cross peak to  $\text{H}^{\text{h}}$ ,  $\text{H}^{\text{f}}$  &  $\text{H}^{\text{d}}$

## Thermodynamic Prins cyclisation of acetaldehyde acetal **281**

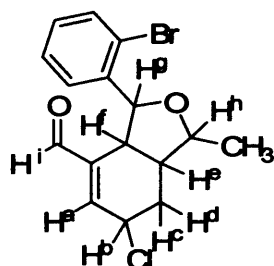


Titanium tetrachloride (2.0 mmol, 0.22 ml, 2 equiv.) was carefully added to a cooled (-78 °C) solution of acetaldehyde acetal **281** (1.0 mmol, 321 mg) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 ml) under a nitrogen atmosphere. The resulting mixture was stirred at this temperature for one hour then at room temperature for 23 h. Saturated NaHCO<sub>3</sub> solution (5 ml) was added then followed by water (20 ml). The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml). The combined extracts were dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to afford a golden yellow solid. Purification by flash chromatography (eluted in gradient mode from EtOAc-hexane 1:9 to 2:8 to 5:5) afforded compound **297** as a pale yellow oil (9 mg, 2.5 %) and compound **298** as a white solid (80 mg, 25 %) respectively.

**(1*SR*,3*RS*,3*aSR*,7*aSR*)-3-(2-Bromophenyl)-6-chloro-1-methyl-1,3,3*a*,6,7,7*a*-hexahydro-isobenzofuran-4-carbaldehyde (**297**):** Yellow oil (9 mg, 2.5 %) (Found:  $M^+$  354.0016. C<sub>16</sub>H<sub>16</sub>O<sub>2</sub><sup>79</sup>Br<sup>35</sup>Cl requires  $M$ , 354.0017);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 2925, 2851, 1693, 1469, 1440, 1379, 1266, 1213, 1164, 1077, 1013, 892;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 9.38 (1 H, s, H<sup>i</sup>), 7.50 (1 H, dd,  $J$  7.7, 1.5, aromatic CH), 7.36 – 7.29 (2 H, m, 2 × aromatic CH), 7.07 (1 H, app. td,  $J$  7.7, 1.7, aromatic CH), 6.74 (1 H, d,  $J$  5.0, H<sup>a</sup>), 5.04 (1 H, d,  $J$  9.5, H<sup>b</sup>), 4.97 – 4.92 (1 H, m, H<sup>b</sup>), 4.72 (1 H, app. dq,  $J$  6.4, 4.6, H<sup>h</sup>), 3.23 (1 H, dd,  $J$  9.5, 5.8, ring junction H<sup>f</sup>), 2.59 (1 H, app. dq,  $J$  10.8, 5.4, ring junction H<sup>e</sup>), 2.20 – 2.14 (2 H, m, ring H<sup>c</sup> and H<sup>d</sup>), 1.27 (3 H, d,  $J$  6.4, CH<sub>3</sub>);  $\delta_C$  (100 MHz; CDCl<sub>3</sub>) 191.8 (O=CH), 144.1 (alkene CH), 141.8 (C<sub>q</sub>=CH), 140.6 (aromatic C<sub>q</sub>), 132.3 (aromatic CH), 129.1 (aromatic CH), 128.0 (aromatic CH), 127.7 (aromatic CH), 122.6 (C<sub>q</sub>-Br), 82.5 (Ar-CH), 78.5 (O-CH-CH<sub>3</sub>), 52.1 (CH-Cl), 45.2 (ring junction CH-CH-Ar), 37.2 (ring junction CH-CH<sub>2</sub>-CH-Cl), 28.3 (ring

CH<sub>2</sub>), 16.0 (CH<sub>3</sub>); *m/z* (APCI) 359 (MH<sup>+</sup> (<sup>81</sup>Br <sup>37</sup>Cl), 20 %), 357 (59), 355 (37), 323 (16), 321 (39), 319 (30), 277 (23), 275 (29), 201 (30), 199 (100), 179 (39), 171 (37), 165 (32), 153 (23), 149 (16).

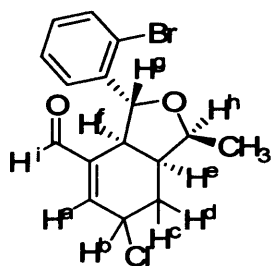
<sup>1</sup>H – <sup>1</sup>H COSY experiment showed the following correlations



297

H<sup>a</sup>, δ = 6.74, showed a cross peak to H<sup>b</sup>  
H<sup>b</sup>, δ = 4.97 - 4.92, showed a cross peak to H<sup>a</sup>, H<sup>f</sup> & H<sup>d</sup>  
H<sup>f</sup> & H<sup>d</sup>, δ = 2.20 - 2.14, showed a cross peak to H<sup>b</sup> & H<sup>e</sup>  
H<sup>e</sup>, δ = 2.59, showed a cross peak to H<sup>f</sup>, H<sup>d</sup>, H<sup>g</sup> & H<sup>h</sup>  
H<sup>g</sup>, δ = 3.23, showed a cross peak to H<sup>b</sup> & H<sup>e</sup>  
H<sup>h</sup>, δ = 5.04, showed a cross peak to H<sup>f</sup>  
H<sup>i</sup>, δ = 4.72, showed a cross peak to H<sup>e</sup> & CH<sub>3</sub>  
CH<sub>3</sub>, δ = 1.27, showed a cross peak to H<sup>i</sup>

NOESY experiment showed the following correlations



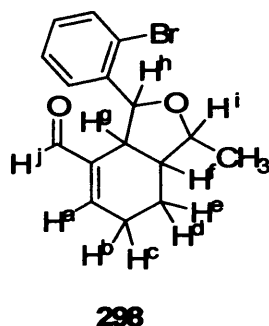
297

H<sup>a</sup>, δ = 6.74, showed a cross peak to H<sup>b</sup> & H<sup>i</sup>  
H<sup>b</sup>, δ = 4.97 - 4.92, showed a cross peak to H<sup>a</sup>, H<sup>f</sup> & H<sup>d</sup>  
H<sup>f</sup> & H<sup>d</sup>, δ = 2.20 - 2.14, showed a cross peak to H<sup>b</sup>, H<sup>e</sup>, H<sup>g</sup> & CH<sub>3</sub>  
H<sup>e</sup>, δ = 2.59, showed a cross peak to H<sup>f</sup> or H<sup>d</sup> or both of them, H<sup>g</sup> & H<sup>h</sup>  
H<sup>g</sup>, δ = 3.23, showed a cross peak to H<sup>i</sup>, H<sup>e</sup> & aromatic H at δ = 7.50 ppm  
H<sup>h</sup>, δ = 5.04, showed a cross peak to H<sup>f</sup> or H<sup>d</sup>  
H<sup>i</sup>, δ = 4.72, showed a cross peak to H<sup>e</sup>, H<sup>g</sup>, & CH<sub>3</sub>  
H<sup>i</sup>, δ = 9.38, showed a cross peak to H<sup>a</sup>  
CH<sub>3</sub>, δ = 1.27, showed a cross peak to H<sup>i</sup>  
Aromatic H, δ = 7.50, showed a cross peak to H<sup>g</sup>

**(1*SR*,3*RS*,3*aSR*,7*aSR*)-3-(2-Bromophenyl)-1-methyl-1,3,3*a*,6,7,7*a*-hexahydro-isobenzofuran-4-carbaldehyde (298)**: white solid (80 mg, 25 %), m.p. 132 - 135 °C (Found: (M+H)<sup>+</sup> 321.0489. C<sub>16</sub>H<sub>18</sub>O<sub>2</sub><sup>79</sup>Br requires M, 321.0485); *v*<sub>max</sub> (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 2942, 1682, 1422, 1378, 1163, 1012; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 9.29 (1 H, s, H<sup>i</sup>), 7.50 (1 H, dd, *J* 7.8, 1.5, aromatic CH), 7.34 (1 H, dd, *J* 8.0, 0.9, aromatic CH), 7.30 (1 H, app. td, *J* 7.5, 0.9, aromatic CH), 7.04 (1 H, app. td, *J* 7.7, 1.5, aromatic CH), 6.81 (1 H, app. dd, *J* 5.0, 2.3, H<sup>a</sup>), 5.07 (1 H, d, *J* 9.5, H<sup>b</sup>), 4.63 (1 H, app. dq, *J* 4.5, 6.4, H<sup>j</sup>), 3.16 (1 H, app. dd, *J* 9.5, 5.8, ring junction H<sup>g</sup>), 2.58 (1 H, app. dt, *J* 20.5, 4.8, H<sup>b</sup>), 2.35 – 2.22 (1 H, m, H<sup>c</sup>), 2.12 (1 H, app. dq, *J* 13.3, 4.6, ring junction H<sup>f</sup>), 1.80 (1 H,

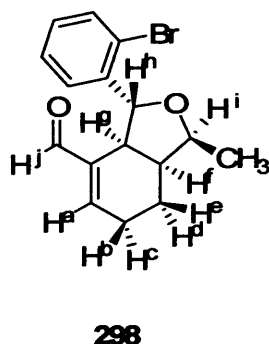
app. dt,  $J$  13.6, 4.9,  $H^d$ ), 1.65 (1 H, app. dq,  $J$  5.4, 13.3,  $H^e$ ), 1.25 (3 H, d,  $J$  6.4,  $CH_3$ );  $\delta_c$  (100 MHz;  $CDCl_3$ ) 192.3 (O=CH), 150.3 (alkene CH), 142.6 ( $C_q=CH$ ), 140.4 (aromatic  $C_q$ ), 132.2 (aromatic CH), 128.8 (aromatic CH), 127.9 (aromatic CH), 127.8 (aromatic CH), 122.8 ( $C_q-Br$ ), 83.1 (Ar-CH), 78.6 (O-CH- $CH_3$ ), 45.6 (Ar-CH-CH), 41.4 (CH- $CH_2-CH_2$ ), 26.1 (=CH- $CH_2-CH_2$ ), 18.8 (=CH- $CH_2-CH_2$ ), 16.0 ( $CH_3$ );  $m/z$  (APCI) 361 ( $M^+$  ( $^{81}Br$ ), 94 %), 321 ( $M^+$  ( $^{79}Br$ ), 100 %), 241 (23), 165 (67), 146 (65).

$^1H - ^1H$  COSY experiment showed the following correlations



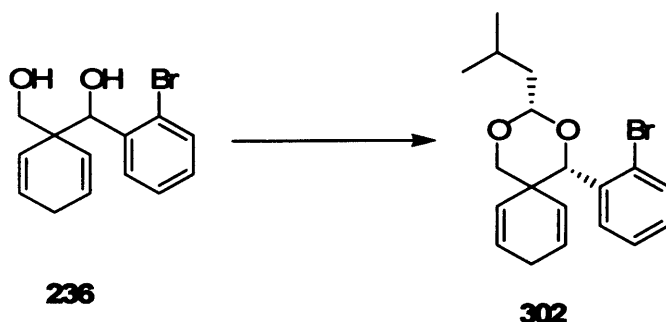
$H^a$ ,  $\delta$  = 6.81, showed a cross peak to  $H^b$  &  $H^f$   
 $H^b$ ,  $\delta$  = 2.58, showed a cross peak to  $H^a$ ,  $H^f$ ,  $H^d$  &  $H^e$   
 $H^f$ ,  $\delta$  = 2.35 - 2.22, showed a cross peak to  $H^a$ ,  $H^b$ ,  $H^d$  &  $H^e$   
 $H^d$ ,  $\delta$  = 1.80, showed a cross peak to  $H^b$ ,  $H^f$ ,  $H^e$  &  $H^i$   
 $H^e$ ,  $\delta$  = 1.65, showed a cross peak to  $H^b$ ,  $H^f$ ,  $H^d$  &  $H^i$   
 $H^i$ ,  $\delta$  = 2.12, showed a cross peak to  $H^b$ ,  $H^f$ ,  $H^d$  &  $H^e$   
 $H^p$ ,  $\delta$  = 3.16, showed a cross peak to  $H^h$  &  $H^f$   
 $H^h$ ,  $\delta$  = 5.07, showed a cross peak to  $H^p$   
 $H^j$ ,  $\delta$  = 4.63, showed a cross peak to  $H^f$  &  $CH_3$   
 $CH_3$ ,  $\delta$  = 1.25, showed a cross peak to  $H^j$

NOESY experiment showed the following correlations



$H^a$ ,  $\delta$  = 6.81, showed a cross peak to  $H^b$ ,  $H^f$  &  $H^j$   
 $H^b$ ,  $\delta$  = 2.58, showed a cross peak to  $H^a$ ,  $H^f$ ,  $H^d$  &  $H^e$   
 $H^f$ ,  $\delta$  = 2.35 - 2.22, showed a cross peak to  $H^a$ ,  $H^b$ ,  $H^d$ ,  $H^e$  &  $H^j$   
 $H^d$ ,  $\delta$  = 1.80, showed a cross peak to  $H^b$ ,  $H^f$ ,  $H^e$  &  $CH_3$   
 $H^e$ ,  $\delta$  = 1.65, showed a cross peak to  $H^b$ ,  $H^f$ ,  $H^d$  &  $CH_3$   
 $H^j$ ,  $\delta$  = 2.12, showed a cross peak to  $H^i$ ,  $H^p$ ,  $H^d$ ,  $H^e$  &  $CH_3$   
 $H^p$ ,  $\delta$  = 3.16, showed a cross peak to aromatic  $H$  at  $\delta$  = 7.50,  $H^h$ ,  $H^i$  &  $H^f$   
 $H^h$ ,  $\delta$  = 5.07, showed a cross peak to  $H^p$  &  $H^e$   
 $H^i$ ,  $\delta$  = 4.63, showed a cross peak to aromatic  $H$  at  $\delta$  = 7.50,  $H^p$ ,  $H^f$  &  $CH_3$   
 $H^j$ ,  $\delta$  = 9.29, showed a cross peak to  $H^a$   
 $CH_3$ ,  $\delta$  = 1.25, showed a cross peak to  $H^i$ ,  $H^f$ ,  $H^d$  &  $H^e$

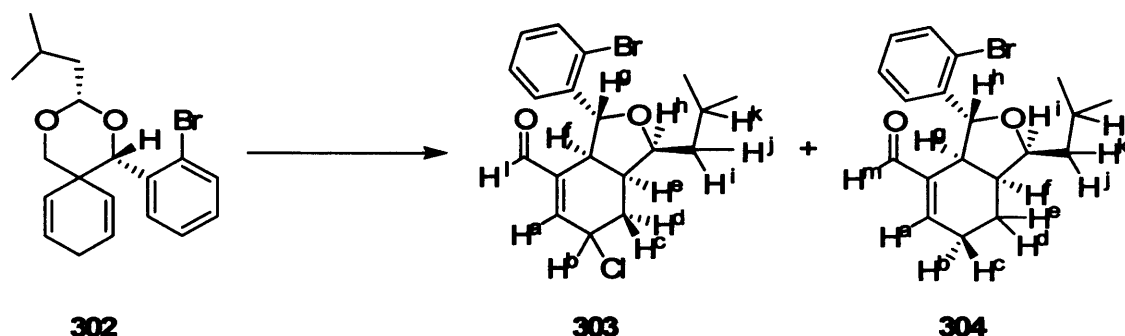
**(1*SR*,3*SR*)-1-(2-Bromophenyl)-3-isobutyl-2,4-dioxaspiro[5.5]undeca-7,10-diene**  
**(302)**



3-Methylbutyraldehyde (4.4 g, 5.5 ml, 50.8 mmol, 10 equiv.) was added to a solution of diol **236** (1.5 g, 5.1 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (25 ml). Pyridinium *p*-toluenesulfonate (0.77 g, 3.05 mmol, 0.6 equiv.) was added and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 4 days. The mixture was poured into water (50 ml) and the organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 30 ml). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford a pale yellow oil. Purification by flash chromatography (eluting with ethyl acetate-hexane 0.5:9.5) afforded the *title compound* (871 mg, 47 %) as a colourless oil;  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3026, 2956, 2923, 2854, 1467, 1439, 1362, 1260, 1128, 1017, 804;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.38 (1 H, dd, *J* 8.0, 1.1, aromatic CH), 7.36 (1 H, dd, *J* 7.8, 1.8, aromatic CH), 7.19 – 7.14 (1 H, m, aromatic CH), 7.00 (1 H, app. td, *J* 7.6, 1.8, aromatic CH), 6.19 (1 H, app. dq, *J* 10.4, 1.9, CH=CH-CH<sub>2</sub>), 5.72 – 5.67 (1 H, m, one of CH=CH-CH<sub>2</sub>), 5.65 – 5.59 (1 H, m, one of CH=CH-CH<sub>2</sub>), 5.49 (1 H, app. dq, *J* 10.2, 1.9, one of CH=CH-CH<sub>2</sub>), 5.05 (1 H, s, CH-Ar), 4.82 (1 H, t, *J* 5.4, O-CH-O), 3.81 and 3.74 (2 H, AB quartet, *J* 11.0, O-CH<sub>2</sub>), 2.35 (1 H, app. dt, *J* 22.9, 3.7, 1.9, one of ring CH<sub>2</sub>), 1.89 (1 H, app. doubled quintet, *J* 22.9, 2.7, one of ring CH<sub>2</sub>), 1.80 (1 H, app. nonet, *J* 6.7, (CH<sub>3</sub>)<sub>2</sub>CH), 1.64 – 1.48 (2 H, m, ((CH<sub>3</sub>)<sub>2</sub>-CH-CH<sub>2</sub>), 0.88 (3 H, d, *J* 6.7, CH<sub>3</sub>), 0.86 (3 H, d, *J* 6.7, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 137.5 (aromatic C<sub>q</sub>), 131.9 (alkene or aromatic CH), 131.0 (alkene or aromatic CH), 128.9 (alkene or aromatic CH), 128.4 (alkene or aromatic CH), 126.4 (alkene or aromatic CH), 126.3 (alkene or aromatic CH), 126.3 (alkene or aromatic CH), 125.4 (alkene or aromatic CH), 123.5 (C<sub>q</sub>-Br),

102.2 (O-CH-O), 83.8 (O-CH-Ar), 76.5 (O-CH<sub>2</sub>), 43.7 ((CH<sub>3</sub>)<sub>2</sub>-CH-CH<sub>2</sub>), 42.1 (ring C<sub>q</sub>), 26.8 (ring CH<sub>2</sub>), 23.8 ((CH<sub>3</sub>)<sub>2</sub>-CH-CH<sub>2</sub>), 23.2 (CH<sub>3</sub>), 22.8 (CH<sub>3</sub>).

### Thermodynamic Prins cyclisation of isobutyl acetal **302**

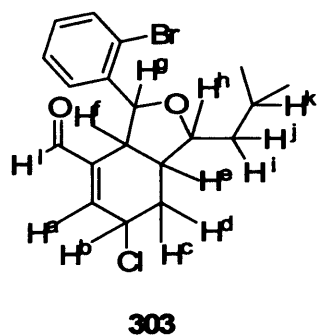


Titanium tetrachloride (2.0 mmol, 0.22 ml, 2 equiv.) was carefully added to a cooled (-78 °C) solution of isobutyl acetal **302** (1.0 mmol, 362 mg) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 ml) under a nitrogen atmosphere. The resulting mixture was stirred at this temperature for one hour then at room temperature for 14 h. Water (20 ml) was added and the organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml). The combined extracts were dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to afford a brown oil. Purification by flash chromatography (eluting with EtOAc-hexane 1:9) afforded compound **303** as a pale yellow solid (32 mg, 8 %) and compound **304** as a yellow oil (91 mg, 25 %) respectively.

**(1*SR*,3*RS*,3*aSR*,7*aSR*)-3-(2-Bromophenyl)-6-chloro-1-isobutyl-1,3,3*a*,7,7*a*-hexahydro-isobenzofuran-4-carbaldehyde (**303**):** Yellow solid (32 mg, 8 %), m.p. 106 – 108 °C;  $\nu_{\text{max}}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 2955, 2855, 2359, 1694, 1468, 1161, 1082, 1021, 753;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 9.38 (1 H, s, H<sup>i</sup>), 7.48 (1 H, app. dd, *J* 8.0, 1.6, aromatic CH), 7.35 - 7.31 (2 H, m, 2 × aromatic CH), 7.07 (1 H, app. td, *J* 7.7, 1.6, aromatic CH), 6.73 (1 H, d, *J* 4.9, H<sup>a</sup>), 5.02 (1 H, d, *J* 9.5, H<sup>g</sup>), 4.95 – 4.91 (1 H, m, H<sup>b</sup>), 4.60 (1 H, app. dt, *J* 8.5, 4.4, H<sup>h</sup>), 3.21 (1 H, dd, *J* 9.5, 5.6, ring junction H<sup>f</sup>), 2.60 (1 H, app. tt, *J* 8.4, 5.1, ring junction H<sup>e</sup>), 2.19 – 2.14 (2 H, m, ring H<sup>c</sup> and H<sup>d</sup>), 1.74 (1 H, app. nonet, *J* 6.7, H<sup>k</sup>), 1.58 – 1.43 (1 H, m, H<sup>j</sup>), 1.36 (1 H, app. ddd, *J* 13.6, 7.6, 5.3, H<sup>j</sup>), 0.93 (6 H, app. t, *J* 6.7, 2 × CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 191.8 (O=CH), 144.0 (alkene CH), 142.1 (C<sub>q</sub>=CH), 140.7 (aromatic C<sub>q</sub>), 132.2 (aromatic CH), 129.1

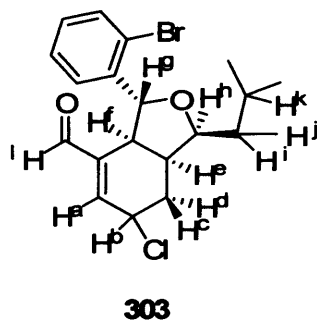
(aromatic CH), 128.0 (aromatic CH), 127.7 (aromatic CH), 122.6 (C<sub>q</sub>-Br), 82.4 (Ar-CH), 81.1 (O-CH), 52.2 (CH-Cl), 45.2 (Ar-CH-CH), 39.6 (CH<sub>2</sub>-CH(CH<sub>3</sub>)<sub>2</sub>), 36.7 (O-CH-CH), 28.4 (ring CH<sub>2</sub>), 25.6 (CH(CH<sub>3</sub>)<sub>2</sub>), 23.4 (CH<sub>3</sub>), 22.6 (CH<sub>3</sub>).

<sup>1</sup>H – <sup>1</sup>H COSY experiment showed the following correlations



H<sup>p</sup>, δ = 6.73, showed a cross peak to H<sup>p</sup>  
H<sup>p</sup>, δ = 4.95 - 4.91, showed a cross peak to H<sup>a</sup>, H<sup>f</sup> & H<sup>d</sup>  
H<sup>f</sup> & H<sup>d</sup>, δ = 2.19 - 2.14, showed a cross peak to H<sup>p</sup> & H<sup>p</sup>  
H<sup>p</sup>, δ = 2.60, showed a cross peak to H<sup>c</sup>, H<sup>d</sup>, H<sup>f</sup> & H<sup>h</sup>  
H<sup>f</sup>, δ = 3.21, showed a cross peak to H<sup>p</sup> & H<sup>p</sup>  
H<sup>p</sup>, δ = 5.02, showed a cross peak to H<sup>f</sup>  
H<sup>h</sup>, δ = 4.60, showed a cross peak to H<sup>i</sup>, H<sup>j</sup> & H<sup>e</sup>  
H<sup>k</sup>, δ = 1.74, showed a cross peak to H<sup>i</sup>, H<sup>j</sup> & CH<sub>3</sub>  
H<sup>i</sup>, δ = 1.58 - 1.43, showed a cross peak to H<sup>j</sup>, H<sup>h</sup> & H<sup>k</sup>  
H<sup>j</sup>, δ = 1.36, showed a cross peak to H<sup>i</sup>, H<sup>h</sup> & H<sup>k</sup>  
CH<sub>3</sub>, δ = 0.93, showed a cross peak to H<sup>k</sup>

The NOESY experiment showed the following correlations



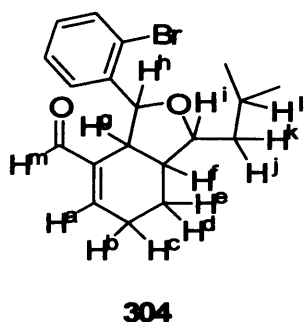
H<sup>p</sup>, δ = 6.73, showed a cross peak to H<sup>p</sup> & H<sup>i</sup>  
H<sup>p</sup>, δ = 4.95 - 4.91, showed a cross peak to H<sup>a</sup>, H<sup>f</sup> & H<sup>d</sup>  
H<sup>f</sup> & H<sup>d</sup>, δ = 2.19 - 2.14, showed a cross peak to H<sup>p</sup>, H<sup>p</sup> & H<sup>p</sup>  
H<sup>p</sup>, δ = 2.60, showed a cross peak to H<sup>c</sup>, H<sup>d</sup>, H<sup>f</sup> & H<sup>h</sup>  
H<sup>f</sup>, δ = 3.21, showed a cross peak to H<sup>p</sup> & H<sup>p</sup>  
H<sup>p</sup>, δ = 5.02, showed a cross peak to H<sup>f</sup> & H<sup>f</sup>  
H<sup>h</sup>, δ = 4.60, showed a cross peak to H<sup>p</sup>, H<sup>f</sup>, CH<sub>3</sub> & aromatic H  
δ = 7.31

**(1*SR*,3*RS*,3*aSR*,7*aSR*)-3-(2-Bromophenyl)-1-isobutyl-1,3,3*a*,6,7,7*a*-hexahydro-isobenzofuran-4-carbaldehyde (304):** Yellow solid (91 mg, 25 %) m.p. 82 - 84 °C; ν<sub>max</sub> (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3056, 2946, 1688, 1639, 1468, 1367, 1265, 1163, 1087, 1024; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 9.28 (1 H, s, H<sup>m</sup>), 7.48 (1 H, dd, *J* 7.8, 1.5, aromatic CH), 7.35 – 7.29 (2 H, m, 2 × aromatic CH), 7.07 – 7.02 (1 H, m, aromatic CH), 6.80 (1 H, app. dd, *J* 4.9, 2.2, H<sup>a</sup>), 5.06 (1 H, d, *J* 9.5, H<sup>b</sup>), 4.51 (1 H, app. dt, *J* 7.8, 4.9, H<sup>i</sup>), 3.13 (1 H, app. dd, *J* 8.8, 5.9, ring junction H<sup>e</sup>), 2.59 (1 H, app. dt, *J* 20.3, 4.9, H<sup>b</sup>), 2.35 – 2.23 (1 H, m, H<sup>c</sup>), 2.18 – 2.07 (1 H, m, ring junction H<sup>f</sup>), 1.85 – 1.60 (3 H, m, H<sup>d</sup>, H<sup>e</sup> and H<sup>j</sup>), 1.60 – 1.48 (1 H, m, H<sup>j</sup>), 1.40 – 1.32 (1 H, m, H<sup>k</sup>), 0.92 (6 H, app. t, *J* 6.1, 2 × CH<sub>3</sub>); δ<sub>C</sub> (100 MHz; CDCl<sub>3</sub>) 192.3 (O=CH), 150.1 (alkene CH), 142.9 (C<sub>q</sub>=CH),



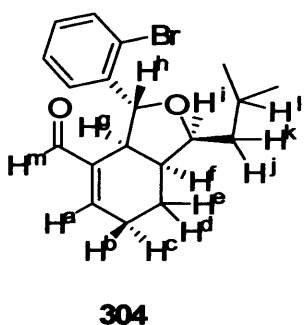
140.5 (aromatic C<sub>q</sub>), 132.2 (aromatic CH), 128.8 (aromatic CH), 127.8 (2 × aromatic CH), 122.8 (C<sub>q</sub>-Br), 82.9 (O-CH-Ar), 81.2 (O-CH-CH), 45.5 (Ar-CH-CH), 40.9 (O-CH-CH), 39.5 (CH<sub>2</sub>-CH(CH<sub>3</sub>)<sub>2</sub>), 26.1 (=CH-CH<sub>2</sub>-CH<sub>2</sub>), 25.6 (CH(CH<sub>3</sub>)<sub>2</sub>), 23.4 (CH<sub>3</sub>), 22.7 (CH<sub>3</sub>), 18.9 (=CH-CH<sub>2</sub>-CH<sub>2</sub>).

<sup>1</sup>H – <sup>1</sup>H COSY experiment showed the following correlations



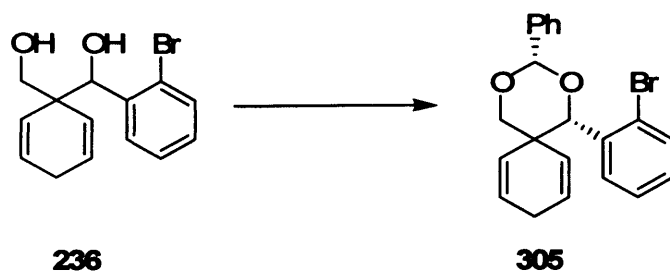
H<sup>a</sup>, δ = 6.80, showed a cross peak to H<sup>b</sup> & H<sup>c</sup>  
H<sup>b</sup>, δ = 2.59, showed a cross peak to H<sup>a</sup>, H<sup>c</sup>, H<sup>d</sup> & H<sup>e</sup>  
H<sup>c</sup>, δ = 2.35- 2.23, showed a cross peak to H<sup>a</sup>, H<sup>b</sup>, H<sup>d</sup> & H<sup>e</sup>  
H<sup>d</sup>, H<sup>e</sup>, H<sup>i</sup>, δ = 1.85 - 1.60, showed a cross peak to H<sup>b</sup>, H<sup>c</sup>, H<sup>f</sup>, H<sup>j</sup>, H<sup>k</sup> & CH<sub>3</sub>  
H<sup>f</sup>, δ = 2.18 - 2.07, showed a cross peak to H<sup>b</sup>, H<sup>i</sup>, H<sup>d</sup> & H<sup>e</sup>  
H<sup>g</sup>, δ = 3.13, showed a cross peak to H<sup>h</sup> & H<sup>f</sup>  
H<sup>h</sup>, δ = 5.06, showed a cross peak to H<sup>g</sup>  
H<sup>i</sup>, δ = 4.51, showed a cross peak to H<sup>f</sup>, H<sup>j</sup>, & H<sup>k</sup>  
H<sup>j</sup>, δ = 1.60 - 1.48, showed a cross peak to H<sup>k</sup>, H<sup>i</sup> & H<sup>l</sup>  
H<sup>k</sup>, δ = 1.40 - 1.32, showed a cross peak to H<sup>j</sup>, H<sup>i</sup> & H<sup>l</sup>  
CH<sub>3</sub>, δ = 0.92, showed a cross peak to H<sup>i</sup>

NOESY experiment showed the following correlations



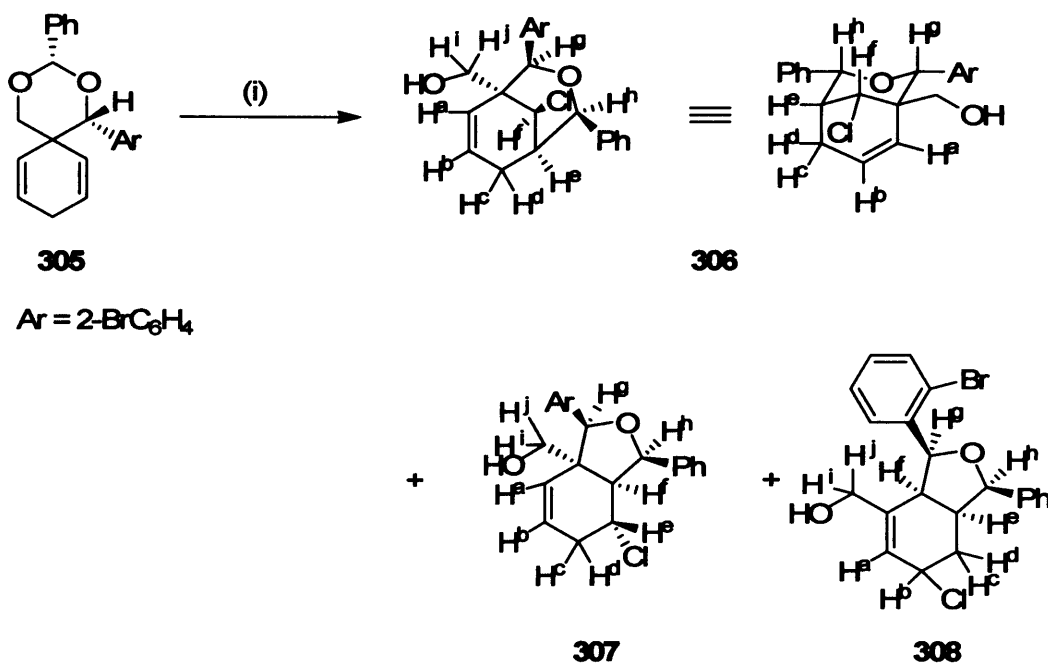
H<sup>m</sup>, δ = 9.28, showed a cross peak to H<sup>a</sup>  
H<sup>a</sup>, δ = 6.80, showed a cross peak to H<sup>b</sup> & H<sup>m</sup>  
H<sup>b</sup>, δ = 2.59, showed a cross peak to H<sup>a</sup>, H<sup>c</sup>, H<sup>d</sup> & H<sup>e</sup>  
H<sup>c</sup>, δ = 2.35- 2.23, showed a cross peak to H<sup>a</sup>, H<sup>b</sup>, H<sup>d</sup>, H<sup>e</sup> & H<sup>f</sup>  
H<sup>d</sup>, H<sup>e</sup>, H<sup>i</sup>, δ = 1.85 - 1.60, showed a cross peak to H<sup>b</sup>, H<sup>c</sup>, H<sup>f</sup>, H<sup>j</sup>, H<sup>k</sup> & CH<sub>3</sub>  
H<sup>f</sup>, δ = 2.18 - 2.07, showed a cross peak to H<sup>b</sup>, H<sup>i</sup>, H<sup>d</sup>, H<sup>e</sup> & H<sup>g</sup>  
H<sup>g</sup>, δ = 3.13, showed a cross peak to H<sup>h</sup>, H<sup>i</sup>, H<sup>f</sup> & aromatic H at δ = 7.48 ppm  
H<sup>h</sup>, δ = 5.06, showed a cross peak to H<sup>g</sup> & (H<sup>e</sup> or H<sup>d</sup> or H<sup>f</sup>)  
H<sup>i</sup>, δ = 4.51, showed a cross peak to H<sup>f</sup>, H<sup>j</sup>, H<sup>k</sup>, H<sup>g</sup> two of aromatic H at δ = 7.48 & CH<sub>3</sub>  
aromatic H at δ = 7.48, showed a cross peak to H<sup>i</sup>, H<sup>g</sup> & two aromatic H δ = 7.35 - 7.29  
H<sup>j</sup>, δ = 1.40 - 1.32, showed a cross peak to H<sup>k</sup>, H<sup>i</sup>, H<sup>l</sup> & two CH<sub>3</sub>  
H<sup>k</sup>, δ = 1.60 - 1.48, showed a cross peak to H<sup>j</sup>, H<sup>i</sup>, H<sup>l</sup> & two CH<sub>3</sub>  
CH<sub>3</sub>, δ = 0.92, showed a cross peak to H<sup>i</sup>, H<sup>j</sup> & H<sup>k</sup>

**(1*SR*,3*SR*)-1-(2-Bromophenyl)-3-phenyl-2,4-dioxaspiro[5.5]undeca-7,10-diene**  
**(305)**



Concentrated sulphuric acid (0.12 ml) was added to a solution of diol **236** (1.0 g, 3.39 mmol) and benzaldehyde (0.7 ml) in DMF (10 ml). The resulting mixture was stirred at room temperature under a nitrogen atmosphere for 6 days. Then the reaction mixture was poured into ice-water (100 ml) containing K<sub>2</sub>CO<sub>3</sub> (180 mg) and the organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 ml). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford a yellow oil. Purification by flash chromatography (eluting with ethyl acetate-hexane 3:7) afforded the *title compound* (716 mg, 55 %) as white crystals, m.p. 104 - 105 °C;  $\nu_{\text{max}}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3022, 2886, 2852, 1449, 1401, 1322, 1223, 1112, 1023, 753;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.82 (2 H, d, *J* 7.8, 2 × aromatic CH), 7.75 (1 H, dd, *J* 7.8, 1.6, aromatic CH), 7.70 (1 H, dd, *J* 8.0, 0.9, aromatic CH), 7.67 – 7.58 (3 H, m, 3 × aromatic CH), 7.48 (1 H, app. t, *J* 7.9, aromatic CH), 7.32 (1 H, app. dt, *J* 7.7, 1.7, aromatic CH), 6.65 (1 H, app. dq, *J* 10.3, 1.6, one of CH=CH-CH<sub>2</sub>), 6.11 – 6.02 (2 H, m, one of CH=CH-CH<sub>2</sub> and O-CH-O), 5.98 (1 H, broad d, *J* 10.1, one of CH=CH-CH<sub>2</sub>), 5.88 (1 H, app. dq, *J* 10.2, 1.7, one of CH=CH-CH<sub>2</sub>), 5.62 (1 H, s, CH-Ar), 4.30 (2 H, app. singlet, O-CH<sub>2</sub>), 2.75 – 2.63 (1 H, m, one of ring CH<sub>2</sub>), 2.29 - 2.18 (1 H, m, one of ring CH<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 138.3 (aromatic C<sub>q</sub>), 137.2 (aromatic C<sub>q</sub>), 131.9 (alkene or aromatic CH), 131.1 (alkene or aromatic CH), 129.1 (alkene or aromatic CH), 128.9 (alkene or aromatic CH), 128.7 (alkene or aromatic CH), 128.3 (2 × aromatic CH), 126.6 (alkene or aromatic CH), 126.4 (alkene or aromatic CH), 126.3 (2 × aromatic CH), 126.1 (alkene or aromatic CH), 125.2 (alkene or aromatic CH), 123.6 (C<sub>q</sub>-Br), 102.5 (O-CH-O), 84.2 (O-CH-Ar), 76.9 (O-CH<sub>2</sub>), 42.3 (ring C<sub>q</sub>), 26.8 (ring CH<sub>2</sub>).

## Prins cyclisation of benzaldehyde acetal **305**

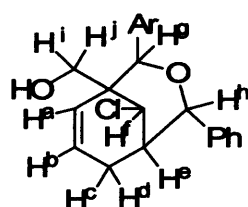


Titanium tetrachloride (1.0 mmol, 0.11 ml, 2 equiv.) was carefully added to a cooled (-78 °C) solution of benzaldehyde acetal **305** (0.5 mmol, 191.6 mg) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 ml) under a nitrogen atmosphere. The resulting mixture was stirred at this temperature for 2 h, then carefully quenched with water (20 ml). The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml). The combined extracts were dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to afford a pale yellow solid. Purification by flash chromatography (eluting with EtOAc-hexane 1:9) afforded compound **306** as a colourless solid (10 mg, 4.8 %), compound **307** as a pale yellow oil (17 mg, 8 %) and compound **308** as a pale yellow solid (97 mg, 46 %) respectively.

**[(1*RS*,2*SR*,4*SR*,5*RS*,9*RS*)-[2-(2-Bromophenyl)-9-chloro-4-phenyl-3-oxa-bicyclo[3.3.1]non-7-en-1-yl]-methanol (**306**):** Colourless solid (10 mg, 4.8 %), m.p. 70 – 72 °C;  $\nu_{\text{max}}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3466, 3061, 3027, 2924, 1472, 1266, 1122, 1071, 1030, 751;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.59 (1 H, dd, *J* 7.9, 1.6, aromatic CH), 7.49 (1 H, dd, *J* 8.0, 0.9, aromatic CH), 7.32 – 7.24 (5 H, m, 5 × aromatic CH), 7.23 – 7.17 (1 H, m, aromatic CH), 7.12 (1 H, app. td, *J* 7.7, 1.7, aromatic CH), 5.99 (1 H, app. dt, *J* 9.9, 3.4, H<sup>b</sup>), 5.16 (1 H, s, H<sup>g</sup>), 4.92 (2 H, broad resonance, H<sup>h</sup> and H<sup>f</sup>), 4.87 (1 H,

app. dd,  $J$  9.9, 1.6,  $H^a$ ), 3.66 (1 H, dd,  $J$  12.3, 7.6,  $H^i$ ), 3.31 (1 H, dd,  $J$  12.3, 4.8,  $H^j$ ), 2.52 – 2.47 (1 H, m, ring junction  $H^e$ ), 2.19 (1 H, app. ddt,  $J$  19.4, 6.7, 2.6,  $H^c$ ), 2.14 – 2.09 (1 H, m, OH), 2.01 - 1.91 (1 H, m,  $H^d$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 139.6 (aromatic  $C_q$ ), 137.5 (aromatic  $C_q$ ), 132.3 (alkene or aromatic CH), 131.6 (alkene or aromatic CH), 130.6 (alkene or aromatic CH), 129.8 (alkene or aromatic CH), 128.3 (2  $\times$  aromatic CH), 127.4 (alkene or aromatic CH), 127.3 (alkene or aromatic CH), 125.6 (2  $\times$  aromatic CH), 123.5 ( $C_q$ -Br), 121.7 (alkene or aromatic CH), 82.4 (O-CH-Ar), 80.9 (O-CH-Ph), 63.2 (O-CH<sub>2</sub>), 62.7 (CH-Cl), 46.6 (ring  $C_q$ ), 41.1 (O-CH-CH), 23.2 (ring CH<sub>2</sub>).

$^1H - ^1H$  COSY experiment showed the following correlations

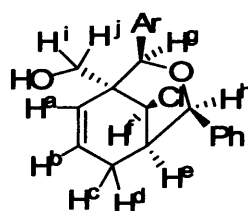


**306**

Ar = 2-BrC<sub>6</sub>H<sub>4</sub>

$H^a$ ,  $\delta$  = 4.87, showed a cross peak to  $H^b$ ,  $H^f$  &  $H^j$   
 $H^b$ ,  $\delta$  = 5.99, showed a cross peak to  $H^a$ ,  $H^f$  &  $H^j$   
 $H^c$ ,  $\delta$  = 2.19, showed a cross peak to  $H^b$ ,  $H^a$ ,  $H^d$  &  $H^e$   
 $H^d$ ,  $\delta$  = 2.01- 2.91, showed a cross peak to  $H^b$ ,  $H^a$  &  $H^e$   
 $H^e$ ,  $\delta$  = 2.52 - 2.47, showed a cross peak to  $H^f$ ,  $H^h$  &  $H^g$   
 $H^f$  &  $H^h$ ,  $\delta$  = 4.92, showed a cross peak to  $H^e$   
 $H^g$ ,  $\delta$  = 5.16, it did not give any cross peaks  
 $H^i$ ,  $\delta$  = 3.66, showed a cross peak to  $H^j$   
 $H^j$ ,  $\delta$  = 3.31, showed a cross peak to  $H^i$

NOESY experiment showed the following correlations



**306**

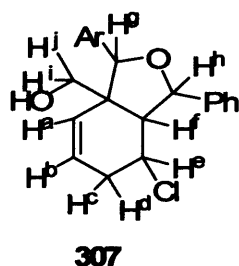
Ar = 2-BrC<sub>6</sub>H<sub>4</sub>Br

$H^a$ ,  $\delta$  = 4.87, showed a cross peak to  $H^b$ ,  $H^i$  &  $H^j$   
 $H^b$ ,  $\delta$  = 5.99, showed a cross peak to  $H^a$ ,  $H^f$  &  $H^j$   
 $H^c$ ,  $\delta$  = 2.19, showed a cross peak to  $H^b$ ,  $H^a$  &  $H^d$   
 $H^d$ ,  $\delta$  = 2.01- 2.91, showed a cross peak to  $H^b$ ,  $H^a$  &  $H^e$   
 $H^e$ ,  $\delta$  = 2.52 - 2.47, showed a cross peak to  $H^f$ ,  $H^d$  and  $H^h$  /  $H^g$   
 $H^f$  &  $H^h$ ,  $\delta$  = 4.92, showed a cross peak to  $H^e$  &  $H^g$   
 $H^g$ ,  $\delta$  = 5.16, showed a cross peak to  $H^f$  /  $H^h$   
 $H^i$ ,  $\delta$  = 3.66, showed a cross peak to  $H^a$ ,  $H^j$  & OH  
 $H^j$ ,  $\delta$  = 3.31, showed a cross peak to  $H^a$ ,  $H^i$  & OH

**[(1*RS*,3*SR*,3*aRS*,7*RS*,7*aSR*)-3-(2-Bromophenyl)-7-chloro-1-phenyl-1,6,7,7*a*-tetrahydro-isobenzofuran-3*a*-yl]-methanol (307):** Pale yellow oil (17 mg, 8 %);  $\nu_{max}$  (neat)/cm<sup>-1</sup> 3450, 3065, 3032, 2931, 1470, 1439, 1374, 1269, 1206, 1067, 1020, 909, 733;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 7.54 (1 H, dd,  $J$  7.9, 1.6, aromatic CH), 7.49 (1 H, dd,  $J$  8.0, 0.9, aromatic CH), 7.42 (2 H, d,  $J$  7.4, 2  $\times$  aromatic CH), 7.35 – 7.22 (4 H,

m, 4 × aromatic CH), 7.12 (1 H, app. td,  $J$  7.6, 1.6, aromatic CH), 5.66 (1 H, app. dt,  $J$  10.2, 4.1,  $H^b$ ), 5.25 (1 H, d,  $J$  7.5,  $H^h$ ), 5.23 (1 H, s, ,  $H^g$ ), 4.81 (1 H, app. dt,  $J$  10.2, 1.7,  $H^g$ ), 4.04 – 4.01 (1 H, m,  $H^e$ ), 3.89 and 3.83 (2 H, AB quartet,  $J$  11.3,  $H^i$  and  $H^j$ ), 3.23 (1 H, app. t,  $J$  7.0, ring junction  $H^f$ ), 2.20 – 2.06 (2 H, m,  $H^c$  and  $H^d$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 137.6 (aromatic  $C_q$ ), 137.2 (aromatic  $C_q$ ), 132.6 (alkene or aromatic CH), 130.9 (alkene or aromatic CH), 129.4 (alkene or aromatic CH), 128.3 (2 × aromatic CH), 127.7 (alkene or aromatic CH), 127.7 (alkene or aromatic CH), 127.2 (alkene or aromatic CH), 127.0 (alkene or aromatic CH), 126.5 (2 × aromatic CH), 122.6 ( $C_q$ -Br), 82.4 (O-CH-Ar), 81.3 (O-CH-Ph), 66.3 (O-CH<sub>2</sub>), 55.4 (CH-Cl), 55.0 (ring  $C_q$ ), 51.3 (O-CH-CH), 32.5 (ring CH<sub>2</sub>).

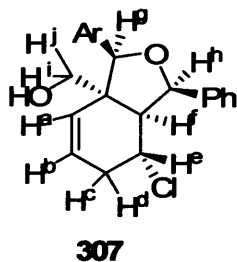
$^1H$  –  $^1H$  COSY experiment showed the following correlations



Ar = 2-BrC<sub>6</sub>H<sub>4</sub>Br

$H^a$ ,  $\delta$  = 4.81, showed a cross peak to  $H^b$ ,  $H^f$  &  $H^d$   
 $H^b$ ,  $\delta$  = 5.66, showed a cross peak to  $H^a$ ,  $H^f$  &  $H^d$   
 $H^c$  &  $H^d$ ,  $\delta$  = 2.20- 2.06, showed a cross peak to  $H^a$ ,  $H^b$  &  $H^f$   
 $H^e$ ,  $\delta$  = 4.04 - 4.01, showed a cross peak to  $H^f$ ,  $H^i$  &  $H^j$   
 $H^f$ ,  $\delta$  = 3.23, showed a cross peak to  $H^i$  &  $H^j$   
 $H^h$ ,  $\delta$  = 5.25, showed a cross peak to  $H^f$

NOESY experiment showed the following correlations



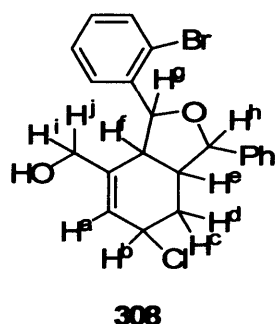
Ar = 2-BrC<sub>6</sub>H<sub>4</sub>Br

$H^a$ ,  $\delta$  = 4.81, showed a cross peak to  $H^b$   
 $H^b$ ,  $\delta$  = 5.66, showed a cross peak to  $H^a$   
 $H^c$  &  $H^d$ ,  $\delta$  = 2.20- 2.06, showed a cross peak to  $H^f$   
 $H^e$ ,  $\delta$  = 4.04 - 4.01, showed a cross peak to  $H^f$  &  $H^d$   
 $H^f$ ,  $\delta$  = 3.23, showed a cross peak to  $H^i$  /  $H^j$   
 $H^g$  /  $H^h$ ,  $\delta$  = 5.25 - 5.23, showed a cross peak to  $H^f$ ,  $H^i$  &  $H^j$   
 $H^i$  &  $H^j$ ,  $\delta$  = 3.89 & 3.83, showed a cross peak to  $H^f$  /  $H^g$

**[(1*RS*,3*SR*,3*aSR*,7*aSR*)-3-(2-Bromophenyl)-6-chloro-1-phenyl-1,3,3*a*,6,7,7*a*-hexahydro-isobenzofuran-4-yl]-methanol (308):** Pale yellow solid (97 mg, 42.6 %) m.p. 50 -52 °C;  $\nu_{max}$  ( $CH_2Cl_2$ )/cm<sup>-1</sup> 3426 (broad), 3061, 3021, 2929, 1732, 1567, 1470, 1367, 1267, 1206, 1121, 916;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 7.82 (2 H, d,  $J$  7.8, 2 ×

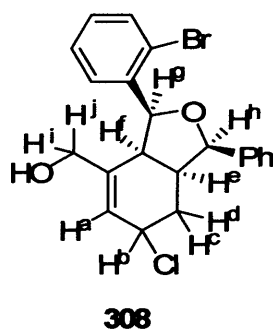
aromatic CH), 7.14 (3 H, m, 3 × aromatic CH), 7.10 – 7.05 (2 H, m, 2 × aromatic CH), 7.05 – 6.99 (2 H, m, 2 × aromatic CH), 6.14 (1 H, d,  $J$  7.4, H<sup>a</sup>), 5.36 (1 H, d,  $J$  5.0, H<sup>b</sup>), 5.25 (1 H, d,  $J$  9.2, H<sup>b</sup>), 3.53 (1 H, app. t,  $J$  5.7, H<sup>f</sup>), 3.40 – 3.32 (1 H, m, H<sup>c</sup>), 3.32 – 3.26 (1 H, m, H<sup>b</sup>), 2.93 and 2.84 (2 H, AB quartet,  $J$  13.5, H<sup>i</sup> and H<sup>j</sup>), 2.01 – 1.89 (2 H, m, H<sup>c</sup> and H<sup>d</sup>);  $\delta_C$  (100 MHz; CDCl<sub>3</sub>) 139.0 (alkene or aromatic C<sub>q</sub>), 136.4 (alkene or aromatic C<sub>q</sub>), 135.9 (alkene or aromatic C<sub>q</sub>), 132.6 (alkene or aromatic CH), 132.2 (alkene or aromatic CH), 130.9 (alkene or aromatic CH), 130.8 (alkene or aromatic CH), 129.1 (alkene or aromatic CH), 128.6 (alkene or aromatic CH), 127.6 (alkene or aromatic CH), 127.6 (alkene or aromatic CH), 127.0 (alkene or aromatic CH), 126.7 (alkene or aromatic CH), 121.3 (C<sub>q</sub>-Br), 83.6 (CH-Ar), 77.6 (CH-Ph), 64.7 (O-CH<sub>2</sub>), 44.1 (CH-Cl), 37.7 (CH-CH-Ar), 35.1 (CH-CH-Ph), 29.6 (ring CH<sub>2</sub>).

<sup>1</sup>H – <sup>1</sup>H COSY experiment showed the following correlations



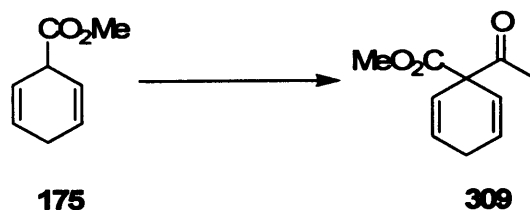
H<sup>a</sup>,  $\delta$  = 6.14, showed a cross peak to H<sup>b</sup>  
H<sup>b</sup>,  $\delta$  = 3.32 – 3.262, showed a cross peak to H<sup>a</sup>, H<sup>c</sup> & H<sup>d</sup>  
H<sup>c</sup> & H<sup>d</sup>,  $\delta$  = 2.01– 1.89, showed a cross peak to H<sup>b</sup> & H<sup>e</sup>  
H<sup>e</sup>,  $\delta$  = 3.40 – 3.32, showed a cross peak to H<sup>c</sup>, H<sup>d</sup>, H<sup>h</sup> & H<sup>f</sup>  
H<sup>f</sup>,  $\delta$  = 3.53, showed a cross peak to H<sup>b</sup> & H<sup>e</sup>  
H<sup>g</sup>,  $\delta$  = 5.36, showed a cross peak to H<sup>f</sup>  
H<sup>h</sup>,  $\delta$  = 5.25, showed a cross peak to H<sup>e</sup>  
H<sup>i</sup>,  $\delta$  = 2.93, showed a cross peak to H<sup>j</sup>  
H<sup>j</sup>,  $\delta$  = 2.84, showed a cross peak to H<sup>i</sup>

NOESY experiment showed the following correlations



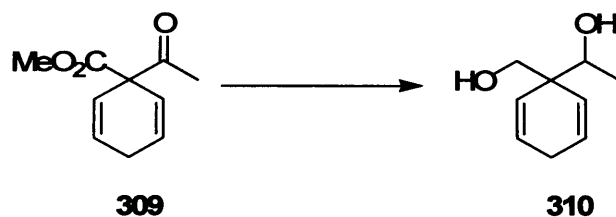
H<sup>a</sup>,  $\delta$  = 6.14, showed a cross peak to H<sup>b</sup>  
H<sup>b</sup>,  $\delta$  = 3.32 – 3.26, showed a cross peak to H<sup>a</sup>, H<sup>c</sup> & H<sup>d</sup>  
H<sup>c</sup> & H<sup>d</sup>,  $\delta$  = 2.01– 1.89, showed a cross peak to H<sup>b</sup> & H<sup>e</sup>  
H<sup>e</sup>,  $\delta$  = 3.40 – 3.32, showed a cross peak to H<sup>c</sup>, H<sup>d</sup>, H<sup>f</sup>, H<sup>g</sup> & H<sup>h</sup>  
H<sup>f</sup>,  $\delta$  = 3.53, showed a cross peak to H<sup>e</sup>, H<sup>h</sup> & H<sup>g</sup>  
H<sup>g</sup>,  $\delta$  = 5.36, showed a cross peak to H<sup>e</sup> & H<sup>f</sup>  
H<sup>h</sup>,  $\delta$  = 5.25, showed a cross peak to H<sup>e</sup> & H<sup>f</sup>

### 1-Acetyl-cyclohexa-2,5-dienecarboxylic methyl ester (309)



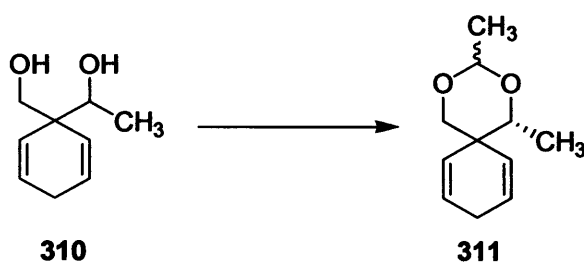
*n*-Butyllithium (2.5 M solution in hexane, 29.0 ml, 72.4 mmol, 1.0 equiv.) was added to a cooled solution of *i*-Pr<sub>2</sub>NH (10.14 ml, 72.4 mmol, 1.0 equiv.) in dry THF (100 ml) at  $-78\text{ }^{\circ}\text{C}$ . After stirring the resulting mixture for 30 min, a solution of ester **175** (10 g, 72.4 mmol, 1.0 equiv.) in THF (10 ml) was added and the stirring was continued for another 30 min. Acetyl chloride (5.7 ml, 79.6 mmol, 1.1 equiv) was added carefully and the reaction mixture was stirred for one hour at  $-78\text{ }^{\circ}\text{C}$ , then at room temperature for 18 h. Saturated ammonium chloride solution (20 ml) was added and the product was extracted three times with  $\text{CH}_2\text{Cl}_2$  (40 ml). The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to afford a yellow oil. Purification by flash chromatography (eluting with ethyl acetate-hexane 1:9) afforded the *title compound* (8.5 g, 65 %) as oil which solidified on standing to white crystals, m.p.  $36 - 38\text{ }^{\circ}\text{C}$ ;  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3042, 2953, 2883, 1720, 1634, 1433, 1354, 1229, 1181, 1071, 942, 797;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.99 – 5.92 (2 H, m,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 5.90 – 5.84 (2 H, m,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 3.64 (3 H, s, O- $\text{CH}_3$ ), 2.74 – 2.57 (2H, m, ring  $\text{CH}_2$ ), 2.07 (3 H, s,  $\text{CH}_3-\text{C}=\text{O}$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 204.8 ( $\text{C}=\text{O}$ ), 170.8 (O- $\text{C}=\text{O}$ ), 128.4 ( $2 \times$  alkene CH), 122.7 ( $2 \times$  alkene CH), 62.9 (ring  $\text{C}_q$ ), 52.7 (O- $\text{CH}_3$ ), 26.1 (ring  $\text{CH}_2$ ), 26.0 ( $\text{CH}_3-\text{C}=\text{O}$ ).

### 1-(1-Hydroxymethyl-cyclohexa-2,5-dienyl)-ethanol (310)



Keto ester **309** (7.2 g, 39.8 mmol) in dry THF (10 ml) was carefully added to a stirred suspension of  $\text{LiAlH}_4$  (4.6 g, 122.4 mmol, 4.1 equiv.) in dry THF (30 ml) under a nitrogen atmosphere at room temperature in a flame-dried flask. After stirring for 18 h, 15 % aqueous NaOH solution (4.7 ml) was added carefully followed by water (13.7 ml) and the stirring was continued at room temperature for two hours. Filtration and concentration under reduced pressure afforded a viscous yellow oil. Purification by flash chromatography (eluting with hexane-ethyl acetate 1:1) afforded the *title diol* (4.98 g, 81 %) as a colourless solid, m.p. 50 – 52 °C;  $\nu_{\text{max}}$  ( $\text{CH}_2\text{Cl}_2$ )/ $\text{cm}^{-1}$  3394 (broad), 3022, 2973, 2879, 1635, 1421, 1372, 1130, 1025, 904;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.99 (1 H, m, one of  $\text{CH}=\text{CH}-\text{CH}_2$ ), 5.88 (1 H, m, one of  $\text{CH}=\text{CH}-\text{CH}_2$ ), 5.68 (1 H, app. dd,  $J$  10.3, 2.0, one of  $\text{CH}=\text{CH}-\text{CH}_2$ ), 5.36 (1 H, app. dd,  $J$  10.3, 2.0, one of  $\text{CH}=\text{CH}-\text{CH}_2$ ), 3.75 (1 H, q,  $J$  6.4,  $\text{CH}-\text{OH}$ ), 3.58 and 3.50 (2 H, AB quartet,  $J$  10.5,  $\text{CH}_2-\text{OH}$ ), 2.70 – 2.56 (2 H, app. m, ring  $\text{CH}_2$ ), 2.52 (2 H, broad s, 2  $\times$  OH), 1.04 (3 H, d,  $J$  6.4,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 128.4 (alkene CH), 127.9 (alkene CH), 127.0 (alkene CH), 125.5 (alkene CH), 72.9 ( $\text{CH}-\text{OH}$ ), 69.6 ( $\text{CH}_2-\text{OH}$ ), 46.7 (ring  $\text{C}_q$ ), 27.2 (ring  $\text{CH}_2$ ), 19.1 ( $\text{CH}_3$ ).

### 1,3-Dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (**311**)



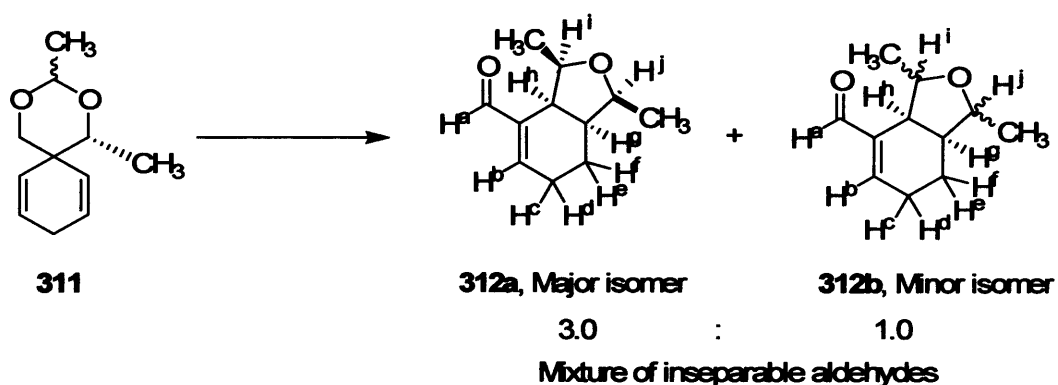
Acetaldehyde (1.86 ml, 33.1 mmol, 5 equiv.) was added to a solution of diol **310** (1.0 g, 6.63 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (20 ml). Pyridinium *p*-toluenesulfonate (666 mg, 2.6 mmol, 0.4 equiv.) was added and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 48 h. Then another 2 equivalent of acetaldehyde (0.75 ml, 13.3 mmol) was added and stirring was continued for another 4 days. The mixture was poured into  $\text{H}_2\text{O}$  (30 ml) and the organic material was extracted into  $\text{CH}_2\text{Cl}_2$  (2  $\times$  30 ml). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to afford pale yellow oil.



Purification by flash chromatography (eluting with hexane-ethyl acetate 9:1) afforded the *title acetal* (mixture of two diastereoisomers) (631 mg, 54 %) as a pale yellow oil;  $\nu_{\max}$  (neat)/ $\text{cm}^{-1}$  3014, 2978, 2840, 1450, 1408, 1377, 1232, 1179, 1145, 1037, 955, 867;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 6.04 – 5.96 (1 H, m, alkene CH), 5.89 – 5.77 (2 H, m, 2  $\times$  alkene CH), 5.09 – 5.01 (1 H, m, alkene CH), 4.70 (1 H, q,  $J$  5.0, O-CH-O), 3.65 (1 H, d,  $J$  11.0, one of O-CH<sub>2</sub>), 3.52 (1 H, q,  $J$  6.3, O-CH-C<sub>q</sub>), 3.45 (1 H, d,  $J$  11.0, one of O-CH<sub>2</sub>), 2.64 - 2.57 (2 H, m, ring CH<sub>2</sub>), 1.30 (3 H, d,  $J$  5.0, CH<sub>3</sub>-CH-O), 1.00 (3 H, d,  $J$  6.3, CH<sub>3</sub>-CH-O);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 128.7 (alkene CH), 126.6 (alkene CH), 126.2 (alkene CH), 125.3 (alkene CH), 99.3 (O-CH-O), 79.2 (O-CH-CH<sub>3</sub>), 76.1 (O-CH<sub>2</sub>), 39.7 (ring C<sub>q</sub>), 27.4 (ring CH<sub>2</sub>), 21.1 (CH<sub>3</sub>), 16.9 (CH<sub>3</sub>).

### Thermodynamic Prins cyclisation of acetaldehyde acetal (311)

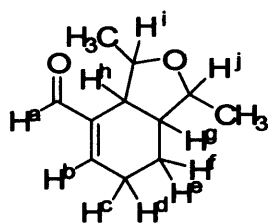
(1*SR*,3*RS*,3*aSR*,7*aSR*)-1,3-Dimethyl-1,3,3*a*,6,7,7*a*-hexahydro-isobenzofuran-4-carbaldehyde (312a) and (unknown stereochemistry) (3*aSR*,7*aSR*)-1,3-Dimethyl-1,3,3*a*,6,7,7*a*-hexahydro-isobenzofuran-4-carbaldehyde (312b)



Titanium tetrachloride (4.0 mmol, 0.44 ml, 2 equiv.) was carefully added to a cooled (-78 °C) solution of acetaldehyde acetal **311** (2.0 mmol, 360.5 mg) in dry  $\text{CH}_2\text{Cl}_2$  (20 ml) under a nitrogen atmosphere. The resulting mixture was stirred at this temperature for one hour then at room temperature for 23 h. water (20 ml) was added and the organic material was extracted into  $\text{CH}_2\text{Cl}_2$  (3  $\times$  20 ml). The combined extracts were dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure to afford brown oil. Purification by flash chromatography (eluting with EtOAc-hexane 1:9)

afforded compound **312** as a mixture of two inseparable diastereomeric aldehydes (133 mg, 37 %) in major:minor ratio (3:1) as a pale yellow solid, m.p. 38 – 56 °C (mixture of two diastereoisomers) (Found: (M+NH<sub>4</sub>)<sup>+</sup> 198.1489. C<sub>11</sub>H<sub>20</sub>O<sub>2</sub>N requires M, 198.1489);  $\nu_{\text{max}}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 2974, 2939, 2879, 1682, 1640, 1457, 1422, 1372, 1216, 1165, 1095, 934;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 9.40 (1 H, s, H<sup>a</sup> of major isomer), 9.38 (1 H, s, H<sup>a</sup> of minor isomer), 6.95 (1 H, app. d, *J* 5.1, H<sup>b</sup> of major isomer), 6.83 (1 H, app. dd, *J* 5.6, 3.2, H<sup>b</sup> of minor isomer), 4.34 (1 H, app. dq, *J* 9.9, 6.4, H<sup>i</sup> of major isomer), 4.20 (1 H, app. dq, *J* 6.3, 4.2, H<sup>j</sup> of minor isomer), 3.97 (1 H, app. dq, *J* 4.1, 6.4, H<sup>j</sup> of major isomer), 3.72 (1 H, app. dq, *J* 7.9, 6.3, H<sup>i</sup> of minor isomer), 3.18 (1 H, app. t, *J* 8.2, ring junction H<sup>h</sup> of major isomer), 2.75 (1 H, app. t, *J* 6.3, ring junction H<sup>h</sup> of minor isomer), 2.53 – 2.42 (2 H, m, H<sup>c</sup> of both isomers), 2.27 – 2.14 (2 H, m, H<sup>d</sup> of both isomers), 1.97 – 1.84 (2 H, m, ring junction H<sup>g</sup> of both isomers), 1.75 – 1.66 (2 H, m, H<sup>e</sup> of both isomers), 1.47 – 1.28 (2 H, m, H<sup>f</sup> of both isomers), 1.35 (3 H, d, *J* 6.3, CH<sub>3</sub> of minor isomer), 1.18 (3 H, d, *J* 6.4, CH<sub>3</sub> of major isomer), 1.16 (3 H, d, *J* 6.3, CH<sub>3</sub> of minor isomer), 0.87 (3 H, d, *J* 6.4, CH<sub>3</sub> of major isomer);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 194.5 (O=CH of major isomer), 194.1 (O=CH of minor isomer), 152.8 (alkene CH of major isomer), 152.6 (alkene CH of minor isomer), 141.7 (alkene C<sub>q</sub> of minor isomer), 140.9 (alkene C<sub>q</sub> of major isomer), 79.5 (O-CH of minor isomer), 76.2 (O-CH of major isomer), 75.6 (O-CH of minor isomer), 74.8 (O-CH of major isomer), 44.0 (ring junction O-CH-CH of minor isomer), 41.3 (ring junction CH-CH<sub>2</sub> of minor isomer), 40.2 (ring junction O-CH-CH of major isomer), 39.4 (ring junction CH-CH<sub>2</sub> of major isomer), 25.9 (=CH-CH<sub>2</sub> of minor isomer), 25.7 (=CH-CH<sub>2</sub> of major isomer), 22.1 (one of CH<sub>3</sub> of minor isomer), 19.8 (one of CH<sub>3</sub> of major isomer), 19.2 (=CH-CH<sub>2</sub>-CH<sub>2</sub> of major isomer), 18.8 (=CH-CH<sub>2</sub>-CH<sub>2</sub> of minor isomer), 15.4 (one of CH<sub>3</sub> of minor isomer), 15.1 (one of CH<sub>3</sub> of major isomer); *m/z* (CI) 198 (M + NH<sub>4</sub><sup>+</sup>, 70 %), 195 (100), 181 (40), 136 (17), 52 (19).

$^1\text{H} - ^1\text{H}$  COSY experiment showed the following correlations for the major isomer

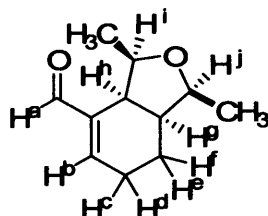


**312a**

Major isomer

$\text{H}^b$ ,  $\delta = 6.95$ , showed a cross peak to  $\text{H}^f$   
 $\text{H}^c$ ,  $\delta = 2.53 - 2.42$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^d$ ,  $\text{H}^e$  &  $\text{H}^f$   
 $\text{H}^d$ ,  $\delta = 2.27 - 2.15$ , showed a cross peak to  $\text{H}^c$ ,  $\text{H}^e$  &  $\text{H}^f$   
 $\text{H}^e$ ,  $\delta = 1.75 - 1.66$ , showed a cross peak to  $\text{H}^c$ ,  $\text{H}^d$ ,  $\text{H}^g$  &  $\text{H}^f$   
 $\text{H}^f$ ,  $\delta = 1.47 - 1.28$ , showed a cross peak to  $\text{H}^c$ ,  $\text{H}^d$ ,  $\text{H}^e$  &  $\text{H}^g$   
 $\text{H}^g$ ,  $\delta = 1.97 - 1.84$ , showed a cross peak to  $\text{H}^e$ ,  $\text{H}^f$ ,  $\text{H}^h$  &  $\text{H}^j$   
 $\text{H}^h$ ,  $\delta = 3.18$ , showed a cross peak to  $\text{H}^i$  &  $\text{H}^g$   
 $\text{H}^i$ ,  $\delta = 4.34$ , showed a cross peak to  $\text{H}^h$  &  $\text{CH}_3$   
 $\text{H}^j$ ,  $\delta = 3.97$ , showed a cross peak to  $\text{H}^g$  &  $\text{CH}_3$   
 $\text{CH}_3$ ,  $\delta = 1.18$ , showed a cross peak to  $\text{H}^j$   
 $\text{CH}_3$ ,  $\delta = 0.87$ , showed cross peak to  $\text{H}^i$

NOESY experiment showed the following correlations of the major isomer

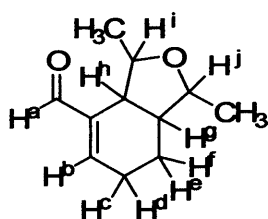


**312a**

Major isomer

$\text{H}^b$ ,  $\delta = 6.95$ , showed a cross peak to  $\text{H}^f$  &  $\text{H}^d$   
 $\text{H}^g$ ,  $\delta = 1.97 - 1.84$ , showed a cross peak to  $\text{H}^e$ ,  $\text{H}^f$ ,  $\text{H}^h$  &  $\text{H}^j$   
 $\text{H}^h$ ,  $\delta = 3.18$ , showed a cross peak to  $\text{H}^i$ ,  $\text{H}^j$  &  $\text{H}^g$   
 $\text{H}^i$ ,  $\delta = 4.34$ , showed a cross peak to  $\text{H}^h$  &  $\text{CH}_3$   
 $\text{H}^j$ ,  $\delta = 3.97$ , showed a cross peak to  $\text{H}^g$ ,  $\text{H}^h$  &  $\text{CH}_3$   
 $\text{CH}_3$ ,  $\delta = 1.18$ , showed a cross peak to  $\text{H}^j$   
 $\text{CH}_3$ ,  $\delta = 0.87$ , showed a cross peak to  $\text{H}^i$

$^1\text{H} - ^1\text{H}$  COSY experiment showed the following correlations of the minor isomer

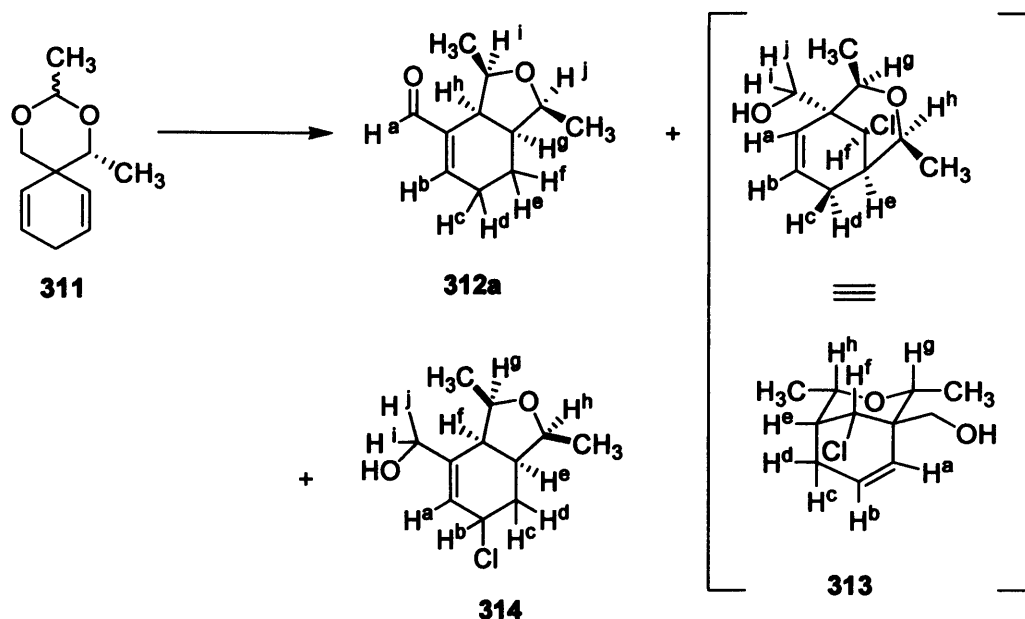


**312b**

Minor isomer

$\text{H}^b$ ,  $\delta = 6.83$ , showed a cross peak to  $\text{H}^f$  &  $\text{H}^d$   
 $\text{H}^c$ ,  $\delta = 2.53 - 2.42$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^d$ ,  $\text{H}^e$  &  $\text{H}^f$   
 $\text{H}^d$ ,  $\delta = 2.27 - 2.15$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^c$ ,  $\text{H}^e$  &  $\text{H}^f$   
 $\text{H}^e$ ,  $\delta = 1.75 - 1.66$ , showed a cross peak to  $\text{H}^c$ ,  $\text{H}^d$ ,  $\text{H}^g$  &  $\text{H}^f$   
 $\text{H}^f$ ,  $\delta = 1.47 - 1.28$ , showed a cross peak to  $\text{H}^c$ ,  $\text{H}^d$ ,  $\text{H}^e$  &  $\text{H}^g$   
 $\text{H}^g$ ,  $\delta = 1.97 - 1.84$ , showed a cross peak to  $\text{H}^e$ ,  $\text{H}^f$ ,  $\text{H}^h$  &  $\text{H}^j$   
 $\text{H}^h$ ,  $\delta = 2.75$ , showed a cross peak to  $\text{H}^i$  &  $\text{H}^g$   
 $\text{H}^i$ ,  $\delta = 3.72$ , showed a cross peak to  $\text{H}^h$  &  $\text{CH}_3$   
 $\text{H}^j$ ,  $\delta = 4.20$ , showed a cross peak to  $\text{H}^g$  &  $\text{CH}_3$   
 $\text{CH}_3$ ,  $\delta = 1.16$ , showed a cross peak to  $\text{H}^j$   
 $\text{CH}_3$ ,  $\delta = 1.35$ , showed a cross peak to  $\text{H}^i$

## Kinetic Prins cyclisation of acetaldehyde acetal **311**



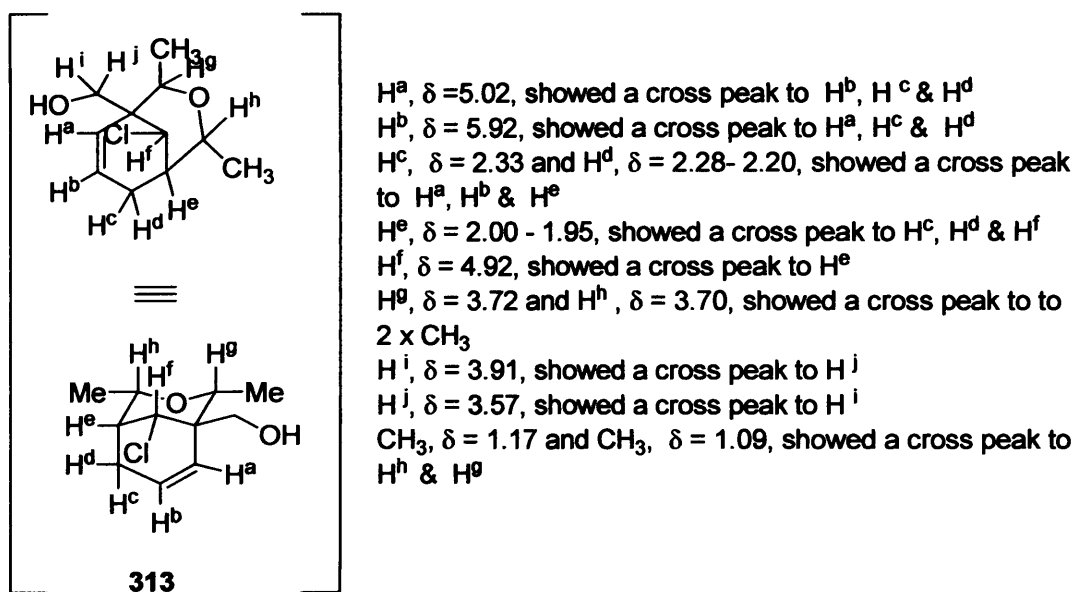
Titanium tetrachloride (1.15 mmol, 0.13 ml, 2 equiv.) was carefully added to a cooled ( $-78\text{ }^{\circ}\text{C}$ ) solution of acetaldehyde acetal **311** (0.58 mmol, 104 mg) in dry  $\text{CH}_2\text{Cl}_2$  (15 ml) under a nitrogen atmosphere. The resulting mixture was stirred at this temperature for 2 h, then carefully quenched with water (20 ml). The organic material was extracted into  $\text{CH}_2\text{Cl}_2$  (2  $\times$  20 ml). The combined extracts were dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure to afford a pale brown oil. Purification by flash chromatography (eluting with EtOAc-hexane 1:9) afforded compound **312a** as a yellow oil (14 mg, 13.5 %) and compound **313** as a pale yellow oil (4 mg, 3.2 %) respectively. While compound **314** was not isolated but its existence was evident from the data obtained from the crude reaction mixture.

**(1*SR*,3*RS*,3*aSR*,7*aSR*)-1,3-Dimethyl-1,3,3*a*,6,7,7*a*-hexahydro-isobenzofuran-4-carbaldehyde (**312a**):** Yellow oil (14 mg, 13.5 %);  $\nu_{\text{max}}$  ( $\text{CH}_2\text{Cl}_2$ )/ $\text{cm}^{-1}$  2924, 1686, 1458, 1375, 1259, 1165;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 9.40 (1 H, s,  $\text{H}^{\text{a}}$ ), 6.95 (1 H, broad singlet,  $\text{H}^{\text{b}}$ ), 4.39 – 4.30 (1 H, m,  $\text{H}^{\text{i}}$ ), 4.02 – 3.94 (1 H, m,  $\text{H}^{\text{j}}$ ), 3.18 (1 H, app. t,  $J$  8.0, ring junction  $\text{H}^{\text{h}}$  of major isomer), 2.54 – 2.42 (1 H, m,  $\text{H}^{\text{c}}$ ), 2.28 – 2.15 (1 H, m,  $\text{H}^{\text{d}}$ ), 2.00 – 1.86 (1 H, m, ring junction  $\text{H}^{\text{e}}$ ), 1.76 – 1.67 (1 H, m,  $\text{H}^{\text{c}}$ ), 1.41 – 1.27 (1 H, m,  $\text{H}^{\text{f}}$ ), 1.18 (3 H, broad singlet,  $\text{CH}_3\text{-H}^{\text{j}}$ ), 0.87 (3 H, d,  $J$  6.4,  $\text{CH}_3\text{-H}^{\text{i}}$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 194.5 ( $\text{O}=\text{CH}$ ), 152.8 (alkene CH), 140.9 (alkene  $\text{C}_{\text{q}}$ ), 76.2 ( $\text{O-CH}$ ),

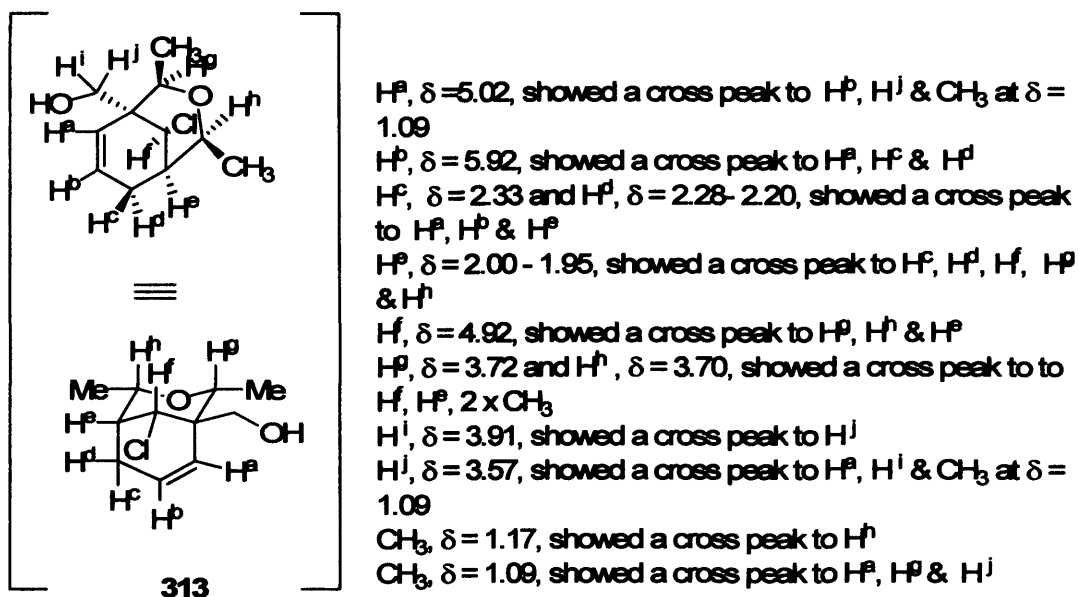
74.8 (O-CH), 40.2 (ring junction O-CH-CH), 39.4 (ring junction CH-CH<sub>2</sub>), 25.7 (=CH-CH<sub>2</sub>), 19.8 (CH<sub>3</sub>), 19.2 (=CH-CH<sub>2</sub>-CH<sub>2</sub>), 15.1 (CH<sub>3</sub>).

**((1*RS*,2*RS*,4*SR*,5*RS*,9*RS*)-9-Chloro-2,4-dimethyl-3-oxa-bicyclo[3.3.1]non-7-en-1-yl)-methanol (313):** Pale yellow oil (4 mg, 3.2 %);  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 5.92 (1 H, app. dt,  $J$  10.0, 3.4, H<sup>b</sup>), 5.02 (1 H, app. dq,  $J$  10.0, 1.8, H<sup>a</sup>), 4.45 (1 H, app. dd,  $J$  3.3, 1.2, H<sup>f</sup>), 3.91 (1 H, d,  $J$  11.2, H<sup>i</sup>), 3.72 (1 H, q,  $J$  6.3, H<sup>g</sup>), 3.70 (3 H, app. dq,  $J$  1.7, 6.4, H<sup>h</sup>), 3.57 (1 H, d,  $J$  11.2, H<sup>j</sup>), 2.33 (1 H, app. ddt,  $J$  19.3, 5.9, 2.9, H<sup>c</sup>), 2.28 – 2.20 (1 H, m, H<sup>d</sup>), 2.00 -1.95 (1 H, m, H<sup>e</sup>), 1.17 (3 H, d,  $J$  6.4, CH<sub>3</sub>-H<sup>h</sup>); 1.09 (3 H, d,  $J$  6.3, CH<sub>3</sub>-H<sup>g</sup>);  $\delta_C$  (100 MHz; CDCl<sub>3</sub>) 130.8 (alkene CH), 121.8 (alkene CH), 76.5 (O-CH), 76.3 (O-CH), 63.5 (O-CH<sub>2</sub>), 63.3 (CH-Cl), 45.6 (ring C<sub>q</sub>), 41.2 (O-CH-CH), 22.7 (ring CH<sub>2</sub>); 19.0 (CH<sub>3</sub>); 16.3 (CH<sub>3</sub>).

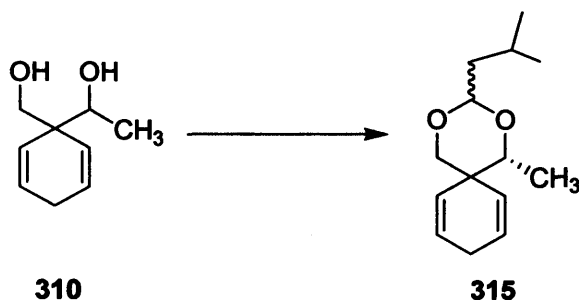
<sup>1</sup>H - <sup>1</sup>H COSY experiment showed the following correlations



NOESY experiment showed the following correlations



### 3-Isobutyl-1-methyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (310)

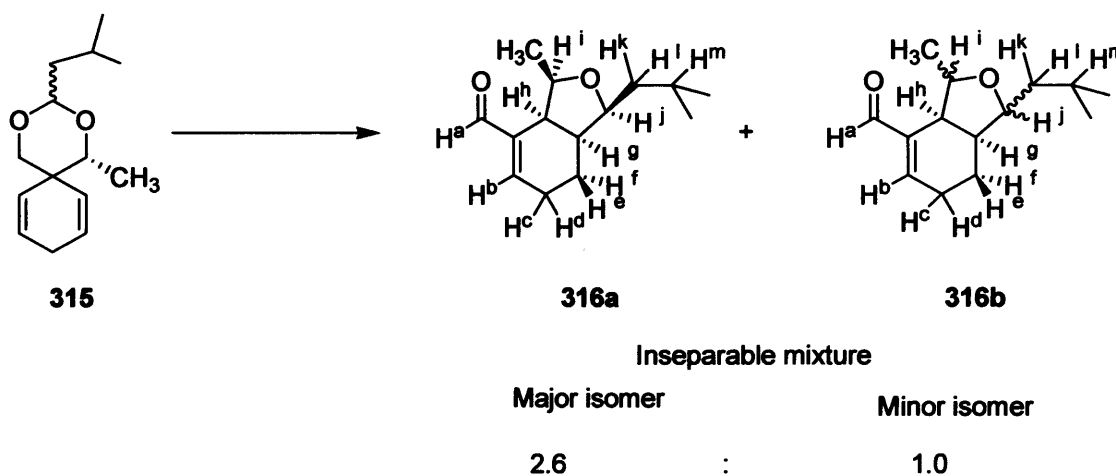


3-Methylbutyraldehyde (4.8 g, 5.9 ml, 50.8 mmol, 10 equiv.) was added to a solution of diol **310** (855 mg, 5.5 mmol) in dry  $CH_2Cl_2$  (25 ml). Pyridinium *p*-toluenesulfonate (834 mg, 3.3 mmol, 0.6 equiv.) was added and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 9 days. The mixture was poured into  $H_2O$  (50 ml) and the organic material was extracted into  $CH_2Cl_2$  ( $2 \times 30$  ml). The combined organic extracts were dried over  $Na_2SO_4$  and concentrated under reduced pressure to afford a yellow oil. Purification by flash chromatography (eluting with ethyl acetate-hexane 0.5:9.5) afforded the *title compound* (mixture of two diastereoisomers) (912 mg, 74 %) as a colourless oil;  $\nu_{max}$  (neat)/ $cm^{-1}$  3017, 2954, 2869, 1454, 1410, 1375, 1261, 1099, 800;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 5.99 (1 H, app. dd,  $J$  10.4, 1.7,  $CH=CH-CH_2$ ), 5.87 – 5.78 (2 H, m,

CH=CH-CH<sub>2</sub>), 5.05 (1 H, app. dd, *J* 10.4, 1.8, CH=CH-CH<sub>2</sub>), 4.58 (1 H, t, *J* 5.4, O-CH-O), 3.66 (1 H, d, *J* 11.0, one of O-CH<sub>2</sub>), 3.50 (1 H, q, *J* 6.4, O-CH-C<sub>q</sub>), 3.45 (1 H, d, *J* 11.0, one of O-CH<sub>2</sub>), 2.70 – 2.53 (2 H, m, ring CH<sub>2</sub>), 1.76 (1 H, app. nonet, *J* 6.8, (CH<sub>3</sub>)<sub>2</sub>-CH), 1.55 – 1.39 (2 H, m, ((CH<sub>3</sub>)<sub>2</sub>-CH-CH<sub>2</sub>), 0.99 (3 H, d, *J* 6.4, CH<sub>3</sub>), 0.85 (6 H, d, *J* 6.6, 2 × CH<sub>3</sub>); δ<sub>c</sub> (100 MHz; CDCl<sub>3</sub>) 128.6 (alkene CH), 126.7 (alkene CH), 126.3 (alkene CH), 125.2 (alkene CH), 101.5 (O-CH-O), 79.3 (O-CH-C<sub>q</sub>), 76.2 (O-CH<sub>2</sub>), 43.7 ((CH<sub>3</sub>)<sub>2</sub>-CH-CH<sub>2</sub>), 39.9 (ring C<sub>q</sub>), 27.4 (ring CH<sub>2</sub>), 23.9 ((CH<sub>3</sub>)<sub>2</sub>-CH-CH<sub>2</sub>), 23.0 (CH<sub>3</sub>), 22.7 (CH<sub>3</sub>), 16.9 (CH<sub>3</sub>).

### Thermodynamic Prins cyclisation of isobutyl acetal 315

**(1*SR*,3*RS*,3*aSR*,7*aSR*)-1-Isobutyl-3-methyl-1,3,3*a*,6,7,7*a*-hexahydro-isobenzofuran-4-carbaldehyde (316a) and (unknown stereochemistry) (3*aSR*,7*aSR*)-1-Isobutyl-3-methyl-1,3,3*a*,6,7,7*a*-hexahydro-isobenzofuran-4-carbaldehyde (316b)**

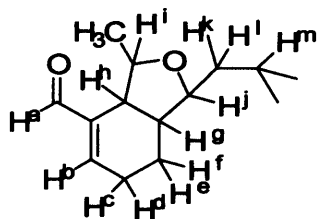


Titanium tetrachloride (1.1 mmol, 0.12 ml, 2 equiv.) was carefully added to a cooled (-78 °C) solution of isobutyl acetal acetal **315** (0.53 mmol, 117 mg) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 ml) under a nitrogen atmosphere. The resulting mixture was stirred at this temperature for one hour then at room temperature for 23 h. Water (20 ml) was added and the organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 ml). The combined extracts were dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to afford a brown oil. Purification by flash chromatography (eluting with EtOAc-hexane 0.7:9.3) afforded compound **316** as a (2.2:1.0) mixture of two inseparable aldehydes (153 mg, 46 %) as a sticky yellow oil; ν<sub>max</sub> (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 2956, 2865, 1682, 1644,

1468, 1371, 1260, 1162, 1095, 951;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 9.39 (1 H, s,  $\text{H}^{\text{a}}$  of major isomer), 9.37 (1 H, s,  $\text{H}^{\text{a}}$  of minor isomer), 6.94 (1 H, app. d,  $J$  4.8,  $\text{H}^{\text{b}}$  of major isomer), 6.82 (1 H, app. dd,  $J$  5.2, 1.7,  $\text{H}^{\text{b}}$  of minor isomer), 4.31 (1 H, app. dq,  $J$  10.0, 6.4,  $\text{H}^{\text{i}}$  of major isomer), 4.10 – 4.04 (1 H, m,  $\text{H}^{\text{j}}$  of minor isomer), 3.85 (1 H, app. ddd,  $J$  7.0, 6.4, 4.1,  $\text{H}^{\text{j}}$  of major isomer), 3.67 (1 H, app. dq,  $J$  7.7, 6.1,  $\text{H}^{\text{i}}$  of minor isomer), 3.15 (1 H, app. t,  $J$  8.0, ring junction  $\text{H}^{\text{h}}$  of major isomer), 2.73 (1 H, app. t,  $J$  6.1, ring junction  $\text{H}^{\text{h}}$  of minor isomer), 2.46 (2 H, app. dt,  $J$  20.1, 5.2,  $\text{H}^{\text{c}}$  of both isomers), 2.29 – 2.14 (2 H, m,  $\text{H}^{\text{d}}$  of both isomers), 2.00 – 1.85 (2 H, m, ring junction  $\text{H}^{\text{e}}$  of both isomers), 1.71 – 1.58 (4 H, m,  $\text{H}^{\text{e}}$  and  $\text{H}^{\text{m}}$  of both isomers), 1.51 – 1.41 (2 H, app. dt,  $J$  7.1, 13.9,  $\text{H}^{\text{k}}$  of both isomers), 1.40 – 1.25 (4 H, m,  $\text{H}^{\text{f}}$  and  $\text{H}^{\text{l}}$  of both isomers), 1.34 (3 H, d,  $J$  6.1,  $\text{CH}_3$  of minor isomer), 0.90 – 0.84 (15 H, m,  $\text{CH}_3$  of major isomer and  $(\text{CH}_3)_2\text{-CH}$  of both isomers);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 194.5 ( $\text{O=CH}$  of major isomer), 194.2 ( $\text{O=CH}$  of minor isomer), 152.8 (alkene CH of major isomer), 152.5 (alkene CH of minor isomer), 141.8 (alkene  $\text{C}_{\text{q}}$  of minor isomer), 141.0 (alkene  $\text{C}_{\text{q}}$  of major isomer), 79.2 ( $\text{O-CH}$  of minor isomer), 78.7 ( $\text{O-CH}$  of major isomer), 78.1 ( $\text{O-CH}$  of minor isomer), 74.5 ( $\text{O-CH}$  of major isomer), 44.0 (ring junction  $\text{O-CH-CH}$  of minor isomer), 40.6 (ring junction  $\text{CH-CH}_2$  of minor isomer), 39.4 (ring junction  $\text{O-CH-CH}$  of major isomer), 39.2 (ring junction  $\text{CH-CH}_2$  of major isomer), 38.9 ( $(\text{CH}_3)_2\text{-CH-CH}_2$  of minor isomer), 38.7 ( $(\text{CH}_3)_2\text{-CH-CH}_2$  of major isomer), 25.9 ( $=\text{CH-CH}_2$  of minor isomer), 25.7 ( $=\text{CH-CH}_2$  of major isomer), 25.6 ( $(\text{CH}_3)_2\text{-CH-CH}_2$  of minor isomer), 25.5 ( $(\text{CH}_3)_2\text{-CH-CH}_2$  of major isomer), 23.3 ( $\text{CH}_3$  of major isomer), 23.2 ( $\text{CH}_3$  of minor isomer), 22.9 ( $\text{CH}_3$  of minor isomer), 22.8 ( $\text{CH}_3$  of major isomer), 22.1 ( $\text{CH}_3$  of minor isomer), 19.9 ( $\text{CH}_3$  of major isomer), 19.3 ( $=\text{CH-CH}_2\text{-CH}_2$  of major isomer), 18.9 ( $=\text{CH-CH}_2\text{-CH}_2$  of minor isomer).



$^1\text{H} - ^1\text{H}$  COSY experiment showed the following correlations of the major isomer

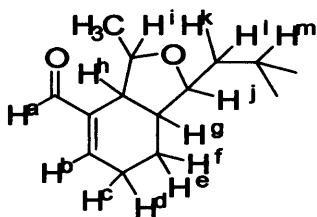


**316a**

Major isomer

$\text{H}^b$ ,  $\delta = 6.94$ , showed a cross peak to  $\text{H}^c$  &  $\text{H}^d$   
 $\text{H}^c$ ,  $\delta = 2.46$ , showed a cross peak to  $\text{H}^d$ ,  $\text{H}^b$  &  $\text{H}^f$   
 $\text{H}^d$ ,  $\delta = 2.29 - 2.14$ , showed a cross peak to  $\text{H}^c$ ,  $\text{H}^b$ ,  $\text{H}^e$  &  $\text{H}^f$   
 $\text{H}^e$  &  $\text{H}^m$ ,  $\delta = 1.71 - 1.58$ , showed a cross peak to  $\text{H}^f$ ,  $\text{H}^d$ ,  $\text{H}^p$ ,  $\text{H}^i$ ,  $\text{H}^k$  &  $2 \times \text{CH}_3$   
 $\text{H}^f$  &  $\text{H}^l$ ,  $\delta = 1.40 - 1.25$ , showed a cross peak to  $\text{H}^e$ ,  $\text{H}^c$ ,  $\text{H}^d$ ,  $\text{H}^p$ ,  $\text{H}^k$ ,  $\text{H}^j$  &  $\text{H}^m$   
 $\text{H}^p$ ,  $\delta = 2.00 - 1.85$ , showed a cross peak to  $\text{H}^e$ ,  $\text{H}^f$ ,  $\text{H}^h$  &  $\text{H}^j$   
 $\text{H}^h$ ,  $\delta = 3.15$ , showed a cross peak to  $\text{H}^i$  &  $\text{H}^p$   
 $\text{H}^i$ ,  $\delta = 4.31$ , showed a cross peak to  $\text{H}^h$  &  $\text{CH}_3$   
 $\text{H}^j$ ,  $\delta = 3.85$ , showed a cross peak to  $\text{H}^p$ ,  $\text{H}^i$  &  $\text{H}^k$   
 $\text{H}^k$ ,  $\delta = 1.51 - 1.41$ , showed a cross peak to  $\text{H}^j$ ,  $\text{H}^i$  &  $\text{H}^m$   
 $\text{CH}_3$  &  $2 \times \text{CH}_3$ ,  $\delta = 0.90 - 0.84$ , showed cross peak to  $\text{H}^i$  &  $\text{H}^m$

$^1\text{H} - ^1\text{H}$  COSY experiment showed the following correlations of the minor isomer

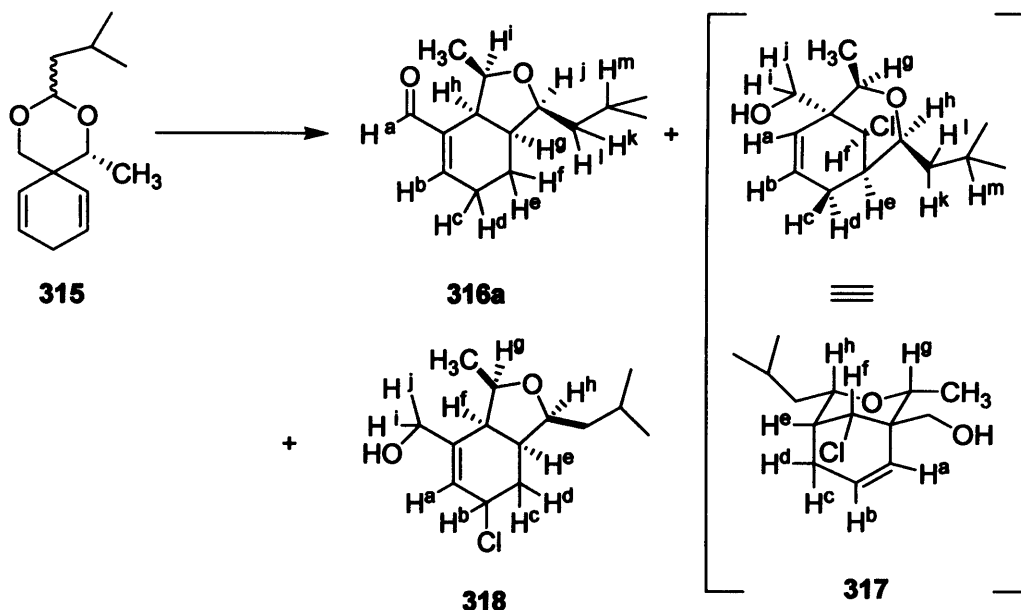


**316b**

Minor isomer

$\text{H}^b$ ,  $\delta = 6.82$ , showed cross peak to  $\text{H}^c$  &  $\text{H}^d$   
 $\text{H}^c$ ,  $\delta = 2.46$ , showed cross peak to  $\text{H}^d$ ,  $\text{H}^b$ ,  $\text{H}^e$  &  $\text{H}^f$   
 $\text{H}^d$ ,  $\delta = 2.29 - 2.14$ , showed cross peak to  $\text{H}^c$ ,  $\text{H}^b$ ,  $\text{H}^e$  &  $\text{H}^f$   
 $\text{H}^e$  &  $\text{H}^m$ ,  $\delta = 1.71 - 1.58$ , showed cross peak to  $\text{H}^f$ ,  $\text{H}^c$ ,  $\text{H}^d$ ,  $\text{H}^p$ ,  $\text{H}^i$ ,  $\text{H}^k$  &  $2 \times \text{CH}_3$   
 $\text{H}^f$  &  $\text{H}^l$ ,  $\delta = 1.40 - 1.25$ , showed cross peak to  $\text{H}^e$ ,  $\text{H}^c$ ,  $\text{H}^d$ ,  $\text{H}^p$ ,  $\text{H}^k$ ,  $\text{H}^j$  &  $\text{H}^m$   
 $\text{H}^p$ ,  $\delta = 2.00 - 1.85$ , showed a cross peak to  $\text{H}^e$ ,  $\text{H}^f$ ,  $\text{H}^h$  &  $\text{H}^j$   
 $\text{H}^h$ ,  $\delta = 2.73$ , showed a cross peak to  $\text{H}^i$  &  $\text{H}^p$   
 $\text{H}^i$ ,  $\delta = 3.67$ , showed a cross peak to  $\text{H}^h$  &  $\text{CH}_3$   
 $\text{H}^j$ ,  $\delta = 4.10 - 4.04$ , showed a cross peak to  $\text{H}^p$ ,  $\text{H}^i$  &  $\text{H}^k$   
 $\text{H}^k$ ,  $\delta = 1.51 - 1.41$ , showed a cross peak to  $\text{H}^j$ ,  $\text{H}^i$  &  $\text{H}^m$   
 $2 \times \text{CH}_3$ ,  $\delta = 0.90 - 0.84$ , showed a cross peak to  $\text{H}^m$   
 $\text{CH}_3$ ,  $\delta = 1.34$ , showed a cross peak to  $\text{H}^i$

## Kinetic Prins cyclisation of isobutyl acetal 315



Titanium tetrachloride (8.0 mmol, 0.9 ml, 2 equiv.) was carefully added to a cooled (-78 °C) solution of isobutyl acetal **315** (4.0 mmol, 889 mg) in dry CH<sub>2</sub>Cl<sub>2</sub> (30 ml) under a nitrogen atmosphere. The resulting mixture was stirred at this temperature for 2 h, then carefully quenched with water (20 ml). The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml). The combined extracts were dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to afford a brown oil. Purification by flash chromatography (eluting with EtOAc-hexane 1:9) afforded compound **316a** as a yellow oil (64 mg, 7 %), and compound **317** as a pale yellow oil (187 mg, 18 %) respectively. While compound **318** was not isolated but its existence was evident from the data obtained from the crude reaction mixture.

### (1*SR*,3*SR*,3*aSR*,7*aSR*)-1-Isobutyl-3-methyl-1,3,3*a*,6,7,7*a*-hexahydro-

**isobenzofuran-4-carbaldehyde (316a):** Yellow oil (64 mg, 7 %);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 2954, 1684, 1642, 1466, 1371, 1093;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 9.39 (1 H, s, H<sup>a</sup>), 6.94 (1 H, app. d,  $J$  5.1, H<sup>b</sup>), 4.31 (1 H, app. dq,  $J$  9.9, 6.4, H<sup>i</sup>), 3.86 (1 H, app. ddd,  $J$  7.3, 6.1, 4.0, H<sup>j</sup>), 3.16 (1 H, app. t,  $J$  8.1, ring junction H<sup>h</sup>), 2.45 (1 H, app. dtd,  $J$  20.0, 4.2, 1.1, H<sup>c</sup>), 2.26 – 2.12 (1 H, m, H<sup>d</sup>), 1.90 (1 H, app. ddt,  $J$  13.1, 6.9, 4.0, H<sup>e</sup>), 1.72 – 1.59 (2 H, m, H<sup>c</sup> and H<sup>m</sup>), 1.47 (1 H, app. dt,  $J$  13.6, 7.2, H<sup>k</sup>), 1.41 – 1.27 (2 H, m, H<sup>f</sup> and H<sup>l</sup>), 0.91 – 0.84 (9 H, m, 3 × CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 194.5 (O=CH), 152.7 (alkene CH), 141.0 (alkene C<sub>q</sub>), 78.7 (O-CH), 74.5 (O-CH), 39.4 (ring junction

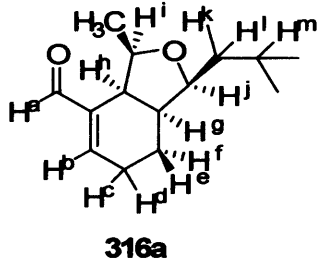
O-CH-CH), 39.2 (ring junction CH-CH<sub>2</sub>), 38.8 ((CH<sub>3</sub>)<sub>2</sub>-CH-CH<sub>2</sub>), 25.7 (=CH-CH<sub>2</sub>), 25.5 ((CH<sub>3</sub>)<sub>2</sub>-CH-CH<sub>2</sub>), 23.3 (CH<sub>3</sub>), 22.8 (CH<sub>3</sub>), 19.8 (CH<sub>3</sub>), 19.3 (=CH-CH<sub>2</sub>-CH<sub>2</sub>).

<sup>1</sup>H – <sup>1</sup>H COSY experiment showed the following correlations



H<sup>a</sup>, δ = 6.94, showed a cross peak to H<sup>c</sup> & H<sup>d</sup>  
H<sup>c</sup>, δ = 2.45, showed a cross peak to H<sup>d</sup>, H<sup>b</sup> & H<sup>f</sup>  
H<sup>d</sup>, δ = 2.26 - 2.12, showed a cross peak to H<sup>c</sup>, H<sup>b</sup>, H<sup>e</sup> & H<sup>f</sup>  
H<sup>e</sup> & H<sup>m</sup>, δ = 1.72 - 1.59, showed a cross peak to H<sup>f</sup>, H<sup>d</sup>, H<sup>b</sup>, H<sup>i</sup>, H<sup>k</sup> & 2 × CH<sub>3</sub>  
H<sup>f</sup> & H<sup>i</sup>, δ = 1.41 - 1.27, showed a cross peak to H<sup>e</sup>, H<sup>c</sup>, H<sup>d</sup>  
H<sup>b</sup>, H<sup>k</sup>, H<sup>j</sup> & H<sup>m</sup>  
H<sup>b</sup>, δ = 1.90, showed a cross peak to H<sup>e</sup>, H<sup>f</sup>, H<sup>i</sup>, & H<sup>j</sup>  
H<sup>i</sup>, δ = 3.16, showed a cross peak to H<sup>j</sup> & H<sup>b</sup>  
H<sup>j</sup>, δ = 4.31, showed a cross peak to H<sup>i</sup> & CH<sub>3</sub>  
H<sup>j</sup>, δ = 3.85, showed a cross peak to H<sup>b</sup>, H<sup>i</sup> & H<sup>k</sup>  
H<sup>k</sup>, δ = 1.47, showed a cross peak to H<sup>j</sup>, H<sup>i</sup> & H<sup>m</sup>  
3 × CH<sub>3</sub>, δ = 0.91 - 0.84, showed cross peak to H<sup>i</sup> & H<sup>m</sup>

NOESY experiment showed the following correlations

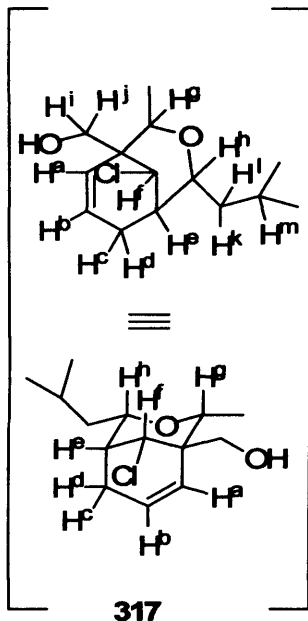


H<sup>a</sup>, δ = 9.39, showed a cross peak to H<sup>b</sup>  
H<sup>b</sup>, δ = 6.94, showed a cross peak to H<sup>a</sup>, H<sup>c</sup> & H<sup>d</sup>  
H<sup>c</sup>, δ = 2.46, showed a cross peak to H<sup>d</sup>, H<sup>b</sup>, H<sup>e</sup> & H<sup>f</sup>  
H<sup>d</sup>, δ = 2.26 - 2.12, showed a cross peak to H<sup>c</sup>, H<sup>b</sup>, H<sup>e</sup> & H<sup>f</sup>  
H<sup>e</sup> & H<sup>m</sup>, δ = 1.72 - 1.59, showed a cross peak to H<sup>f</sup>, H<sup>c</sup>, H<sup>d</sup>, H<sup>i</sup>, H<sup>k</sup> & two CH<sub>3</sub>  
H<sup>f</sup> & H<sup>i</sup>, δ = 1.41 - 1.27, showed a cross peak to H<sup>e</sup>, H<sup>c</sup>, H<sup>d</sup>  
H<sup>b</sup>, H<sup>k</sup>, H<sup>j</sup>, H<sup>m</sup> & 2 × CH<sub>3</sub>  
H<sup>b</sup>, δ = 1.90, showed a cross peak to H<sup>f</sup>, H<sup>j</sup> & H<sup>i</sup>  
H<sup>i</sup>, δ = 3.16, showed a cross peak to H<sup>j</sup>, H<sup>b</sup> & H<sup>j</sup>  
H<sup>j</sup>, δ = 4.31, showed a cross peak to H<sup>i</sup>, H<sup>j</sup> & CH<sub>3</sub>  
H<sup>j</sup>, δ = 3.85 showed a cross peak to H<sup>b</sup>, H<sup>i</sup>, H<sup>k</sup>, H<sup>i</sup>, H<sup>i</sup> & two CH<sub>3</sub>  
3 × CH<sub>3</sub>, δ = 0.91 - 0.84, showed cross peak to H<sup>i</sup>, H<sup>j</sup>, H<sup>k</sup>  
H<sup>i</sup> & H<sup>m</sup>

**((1*RS*,2*RS*,4*SR*,5*RS*,9*RS*)-9-Chloro-4-isobutyl-2-methyl-3-oxa-bicyclo[3.3.1]non-7-en-1-yl)-methanol (317):** Pale yellow oil which solidified on cooling (187, mg, 18 %), m.p. 70 – 72 °C ; ν<sub>max</sub> (neat)/cm<sup>-1</sup> 3442 (broad), 3024, 2955, 1467, 1369, 1107, 1042; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 5.92 (1 H, app. dt, *J* 10.0, 3.5, H<sup>b</sup>), 5.02 (1 H, app. dq, *J* 10.0, 1.9, H<sup>a</sup>), 4.48 (1 H, app. dd, *J* 3.2, 1.3, H<sup>f</sup>), 3.91 (1 H, d, *J* 11.4, H<sup>i</sup>), 3.69 (1 H, q, *J* 6.4, H<sup>e</sup>), 3.57 (1 H, d, *J* 11.4, H<sup>j</sup>), 3.56 – 3.51 (1 H, m, H<sup>h</sup>), 2.32 (1 H, app. ddt, *J* 19.3, 6.0, 2.7, H<sup>c</sup>), 2.24 – 2.16 (1 H, m, H<sup>d</sup>), 2.01 – 1.96 (1 H, m, H<sup>e</sup>), 1.67 (1 H, app. nonet, *J* 6.6, H<sup>m</sup>), 1.53 (1 H, app. ddd, *J* 13.9, 8.4, 6.4, H<sup>k</sup>), 1.16 – 1.10 (1 H, m, H<sup>l</sup>),

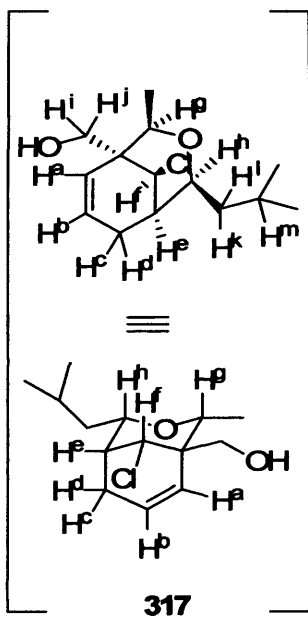
1.08 (3 H, d,  $J$  6.4,  $\text{CH}_3\text{-H}^b$ ), 0.84 (3 H, d,  $J$  6.4, one of  $\text{CH}(\text{CH}_3)_2$ ), 0.83 (3 H, d,  $J$  6.4, one of  $\text{CH}(\text{CH}_3)_2$ );  $\delta_c$  (100 MHz;  $\text{CDCl}_3$ ) 130.9 (alkene CH), 121.9 (alkene CH), 79.1 (O-CH), 76.4 (O-CH), 63.5 (Cl-CH and O- $\text{CH}_2$ ), 45.9 (ring  $\text{C}_q$ ), 42.0 ( $((\text{CH}_3)_2\text{-CH-CH}_2)$ ), 40.2 (ring junction  $\text{CH-CH}_2$ ), 24.6 ( $((\text{CH}_3)_2\text{-CH-CH}_2)$ ), 23.2 ( $=\text{CH-CH}_2$ ), 23.0 ( $\text{CH}_3$ ), 22.5 ( $\text{CH}_3$ ), 16.2 ( $\text{CH}_3$ ).

$^1\text{H} - ^1\text{H}$  COSY experiment showed the following correlations



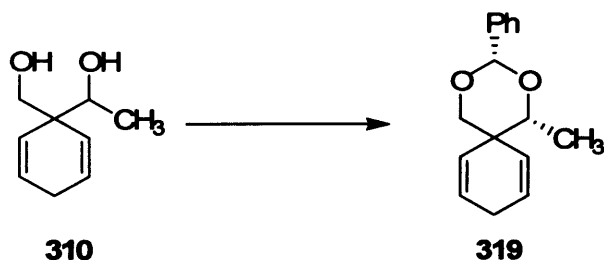
$\text{H}^p$ ,  $\delta = 5.02$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^c$ ,  $\text{H}^d$  &  $\text{H}^f$   
 $\text{H}^b$ ,  $\delta = 5.92$ , showed a cross peak to  $\text{H}^p$ ,  $\text{H}^f$  &  $\text{H}^d$   
 $\text{H}^f$ ,  $\delta = 2.32$ , showed a cross peak to  $\text{H}^p$ ,  $\text{H}^b$ ,  $\text{H}^d$  &  $\text{H}^e$   
 $\text{H}^d$ ,  $\delta = 2.24 - 2.16$ , showed a cross peak to  $\text{H}^p$ ,  $\text{H}^b$  &  $\text{H}^f$   
 $\text{H}^e$ ,  $\delta = 2.01 - 1.96$ , showed a cross peak to  $\text{H}^f$ ,  $\text{H}^d$  &  $\text{H}^h$   
 $\text{H}^f$ ,  $\delta = 4.48$ , showed a cross peak to  $\text{H}^p$  &  $\text{H}^e$   
 $\text{H}^p$ ,  $\delta = 3.69$ , showed a cross peak to  $\text{CH}_3$ ,  $\delta = 1.08$   
 $\text{H}^h$ ,  $\delta = 2.56 - 3.51$ , showed a cross peak to  $\text{H}^k$ ,  $\text{H}^l$  &  $\text{H}^e$   
 $\text{H}^i$ ,  $\delta = 3.91$ , showed a cross peak to  $\text{H}^j$   
 $\text{H}^j$ ,  $\delta = 3.57$ , showed a cross peak to  $\text{H}^i$   
 $\text{H}^k$ ,  $\delta = 1.53$ , showed a cross peak to  $\text{H}^l$ ,  $\text{H}^m$  &  $\text{H}^h$   
 $\text{H}^l$ ,  $\delta = 1.16 - 1.10$ , showed a cross peak to  $\text{H}^k$ ,  $\text{H}^m$  &  $\text{H}^h$   
 $\text{H}^m$ ,  $\delta = 1.67$ , showed a cross peak to  $\text{H}^k$ ,  $\text{H}^l$  & two  $\text{CH}_3$ ,  $\delta = 0.84$  and  $0.83$   
 $\text{CH}_3$ ,  $\delta = 1.08$ , showed a cross peak to  $\text{H}^p$   
 $\text{CH}_3$ ,  $\delta = 0.847$  and  $\text{CH}_3$ ,  $\delta = 0.83$ , showed a cross peak to  $\text{H}^m$

NOESY experiment showed the following correlations



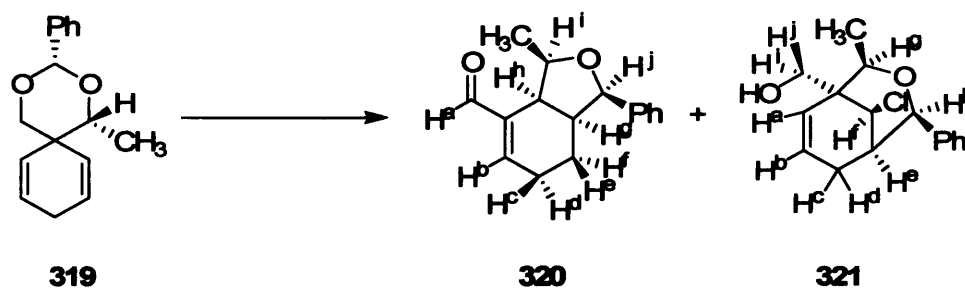
$\text{H}^p$ ,  $\delta = 5.02$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^j$  &  $\text{CH}_3$ ,  $\delta = 1.08$   
 $\text{H}^b$ ,  $\delta = 5.92$ , showed a cross peak to  $\text{H}^p$ ,  $\text{H}^f$  &  $\text{H}^d$   
 $\text{H}^f$ ,  $\delta = 2.32$ , showed a cross peak to  $\text{H}^p$ ,  $\text{H}^d$  &  $\text{H}^e$   
 $\text{H}^d$ ,  $\delta = 2.24 - 2.16$ , showed a cross peak to  $\text{H}^f$ ,  $\text{H}^b$  &  $\text{H}^e$   
 $\text{H}^e$ ,  $\delta = 2.01 - 1.96$ , showed a cross peak to  $\text{H}^f$ ,  $\text{H}^d$ ,  $\text{H}^f$  &  $\text{H}^h$   
 $\text{H}^f$ ,  $\delta = 4.48$ , showed a cross peak to  $\text{H}^p$ ,  $\text{H}^h$  &  $\text{H}^e$   
 $\text{H}^p$ ,  $\delta = 3.69$ , showed a cross peak to  $\text{H}^f$ ,  $\text{H}^h$  &  $\text{CH}_3$ ,  $\delta = 1.08$   
 $\text{H}^h$ ,  $\delta = 2.56 - 3.56$  and  $\text{H}^j$ ,  $\delta = 3.57$  showed a cross peak to  $\text{H}^p$ ,  $\text{H}^f$ ,  $\text{H}^i$ ,  $\text{H}^h$ ,  $\text{H}^e$ ,  $\text{H}^k$  & three  $\text{CH}_3$ ,  $\delta = 1.08$ ,  $0.84$  &  $0.83$   
 $\text{H}^i$ ,  $\delta = 3.91$ , showed a cross peak to  $\text{H}^j$   
 $\text{H}^k$ ,  $\delta = 1.53$ , showed a cross peak to  $\text{H}^l$ ,  $\text{H}^m$ ,  $\text{H}^l$  & two  $\text{CH}_3$ ,  $\delta = 0.847$  and  $0.83$   
 $\text{H}^l$ ,  $\delta = 1.16 - 1.10$  and  $\text{CH}_3$ ,  $\delta = 1.08$ , showed a cross peak to  $\text{H}^p$ ,  $\text{H}^b$ ,  $\text{H}^h$  /  $\text{H}^j$ ,  $\text{H}^m$  &  $\text{H}^k$   
 $\text{H}^m$ ,  $\delta = 1.67$ , showed a cross peak to  $\text{H}^k$ ,  $\text{H}^l$  & two  $\text{CH}_3$ ,  $\delta = 0.84$  and  $0.83$   
 $\text{CH}_3$ ,  $\delta = 0.847$  and  $\text{CH}_3$ ,  $\delta = 0.83$ , showed a cross peak to  $\text{H}^m$  &  $\text{H}^h$

**(1*RS*,3*SR*)-1-Methyl-3-phenyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (319)**



Concentrated sulphuric acid (0.46 ml) was added to a solution of diol **310** (2.0 g, 12.97 mmol) and benzaldehyde (2.83 ml) in DMF (20 ml). The resulting mixture was stirred at room temperature under a nitrogen atmosphere for 7 days. Then the reaction mixture was poured into ice-water (100 ml) containing K<sub>2</sub>CO<sub>3</sub> (690 mg) and the organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3 × 30 ml). The combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford a yellow oil. Purification by flash chromatography (eluting with ethyl acetate-hexane 0.3:9.7) afforded the *title compound* (1.2 g, 38 %) as a colourless oil;  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3033, 2978, 2840, 1452, 1400, 1373, 1161, 1132, 1087, 1021, 970, 746;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.47 (2 H, m, 2 × aromatic CH), 7.33 – 7.23 (3 H, m, 3 × aromatic CH), 6.14 (1 H, app. dq, *J* 10.4, 2.0, one of CH=CH-CH<sub>2</sub>), 5.91 – 5.83 (2 H, m, 2 × CH=CH-CH<sub>2</sub>), 5.50 (1 H, s, O-CH-O), 5.12 (1 H, app. dq, *J* 10.4, 2.0, one of CH=CH-CH<sub>2</sub>), 3.83 (1 H, d, *J* 11.0, one of O-CH<sub>2</sub>), 3.74 (1 H, q, *J* 6.4, O-CH-CH<sub>3</sub>), 3.66 (1 H, d, *J* 11.0, one of O-CH<sub>2</sub>), 2.72 – 2.56 (2 H, m, ring CH<sub>2</sub>), 1.07 (3 H, d, *J* 6.4, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 138.6 (aromatic C<sub>q</sub>), 129.0 (alkene or *p*-aromatic CH), 128.9 (alkene or *p*-aromatic CH), 128.4 (2 × *o*-aromatic CH), 126.6 (alkene), 126.3 (2 × *m*-aromatic CH), 126.2 (alkene CH), 125.4 (alkene CH), 102.0 (O-CH-O), 80.0 (O-CH-CH<sub>3</sub>), 76.6 (O-CH<sub>2</sub>), 39.9 (ring C<sub>q</sub>), 27.5 (ring CH<sub>2</sub>), 17.0 (CH<sub>3</sub>).

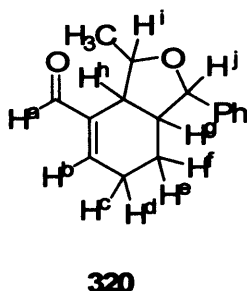
## Prins cyclisation of benzaldehyde acetal 319



Titanium tetrachloride (2.0 mmol, 0.22 ml, 2 equiv.) was carefully added to a cooled (-78 °C) solution of acetaldehyde acetal **319** (1.0 mmol, 242.3 mg) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 ml) under a nitrogen atmosphere. The resulting mixture was stirred at this temperature for 2 h then carefully quenched with water (20 ml). The organic material was extracted into CH<sub>2</sub>Cl<sub>2</sub> (2 × 20 ml). The combined extracts were dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to afford pale brown oil. Purification by flash chromatography (eluting with EtOAc-hexane 1:9) afforded aldehyde **320** as a pale yellow solid (44 mg, 18 %) and alcohol **321** as colourless crystals (70 mg, 25.1%) respectively.

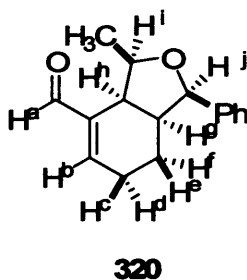
**(1*RS*,3*RS*,3*aSR*,7*aSR*)-3-Methyl-1-phenyl-1,3,3*a*,6,7,7*a*-hexahydro-isobenzofuran-4-carbaldehyde (**320**):** Pale yellow crystalline solid (44 mg, 18 %), m.p. 94 – 96 °C (Found: (M+Na)<sup>+</sup> 265.1200. C<sub>16</sub>H<sub>18</sub>O<sub>2</sub>Na requires M, 265.1199);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 2966, 2925, 2885, 2805, 1671, 1637, 1449, 1172, 1092, 1027;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 9.40 (1 H, s, H<sup>a</sup>), 7.27 (4 H, app. d, *J* 4.4, 4 × aromatic CH), 7.22 – 7.15 (1 H, m, aromatic CH), 6.94 (1 H, app. d, *J* 4.8, H<sup>b</sup>), 5.04 (1 H, d, *J* 4.4, H<sup>j</sup>), 4.57 (1 H, app. dq, *J* 10.0, 6.4, H<sup>i</sup>), 3.39 (1 H, app. t, *J* 8.2, H<sup>h</sup>), 2.35 (1 H, app. dtd, *J* 20.0, 5.3, 1.3, H<sup>c</sup>), 2.21 (1 H, app. ddt, *J* 13.1, 6.8, 4.6, ring junction H<sup>e</sup>), 2.14 – 2.02 (1 H, m, H<sup>d</sup>), 1.18 (1 H, app. dq, *J* 13.3, 5.3, H<sup>e</sup>), 1.09 – 1.01 (1 H, m, H<sup>f</sup>), 0.99 (3 H, d, *J* 6.4, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 194.3 (H-C=O), 152.9 (=CH), 140.8 (alkene C<sub>q</sub>), 138.9 (aromatic C<sub>q</sub>), 128.1 (2 × *o*-aromatic CH), 127.0 (*p*-aromatic CH), 125.9 (2 × *m*-aromatic CH), 82.1 (O-CH-Ph), 75.1 (O-CH-CH<sub>3</sub>), 41.6 (CH=C<sub>q</sub>-CH), 39.6 (CH-CH<sub>2</sub>-CH<sub>2</sub>), 25.7 (=CH-CH<sub>2</sub>), 20.2 (CH-CH<sub>2</sub>), 20.0 (CH<sub>3</sub>); *m/z* (APCI) 260 (M + NH<sub>4</sub><sup>+</sup>, 100 %), 257 (54), 198 (13).

$^1\text{H} - ^1\text{H}$  COSY experiment showed the following correlations



$\text{H}^b$ ,  $\delta = 6.94$ , showed a cross peak to  $\text{H}^c$   
 $\text{H}^c$ ,  $\delta = 2.35$ , showed a cross peak to  $\text{H}^d$ ,  $\text{H}^b$  &  $\text{H}^e$   
 $\text{H}^d$ ,  $\delta = 2.14 - 2.02$ , showed a cross peak to  $\text{H}^c$ ,  $\text{H}^e$  &  $\text{H}^f$   
 $\text{H}^e$ ,  $\delta = 1.18$ , showed a cross peak to  $\text{H}^f$ ,  $\text{H}^c$ ,  $\text{H}^d$  &  $\text{H}^g$   
 $\text{H}^f$ ,  $\delta = 1.09 - 1.01$ , showed a cross peak to  $\text{H}^e$ ,  $\text{H}^d$  &  $\text{H}^g$   
 $\text{H}^g$ ,  $\delta = 2.21$ , showed a cross peak to  $\text{H}^e$ ,  $\text{H}^f$ ,  $\text{H}^h$  &  $\text{H}^i$   
 $\text{H}^h$ ,  $\delta = 3.39$ , showed a cross peak to  $\text{H}^i$  &  $\text{H}^g$   
 $\text{H}^i$ ,  $\delta = 4.57$ , showed a cross peak to  $\text{H}^h$  &  $\text{CH}_3$   
 $\text{H}^j$ ,  $\delta = 5.04$ , showed a cross peak to  $\text{H}^g$   
 $\text{CH}_3$ ,  $\delta = 0.99$ , showed a cross peak to  $\text{H}^i$

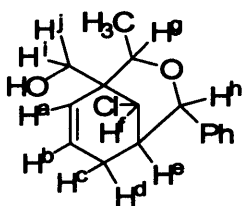
NOESY experiment showed the following correlations



$\text{H}^b$ ,  $\delta = 6.94$ , showed a cross peak to  $\text{H}^c$  &  $\text{H}^d$   
 $\text{H}^c$ ,  $\delta = 2.35$ , showed a cross peak to  $\text{H}^e$ ,  $\text{H}^d$  &  $\text{H}^b$   
 $\text{H}^d$ ,  $\delta = 2.14 - 2.02$ , showed a cross peak to  $\text{H}^c$ ,  $\text{H}^e$  &  $\text{H}^f$   
 $\text{H}^e$ ,  $\delta = 1.18$ , showed a cross peak to  $\text{H}^c$  &  $\text{H}^f$   
 $\text{H}^f$ ,  $\delta = 1.09 - 1.01$ , showed a cross peak to  $\text{H}^g$ ,  $\text{H}^d$  &  $\text{H}^e$   
 $\text{H}^g$ ,  $\delta = 2.21$ , showed a cross peak to  $\text{H}^f$ ,  $\text{H}^h$  &  $\text{H}^i$   
 $\text{H}^h$ ,  $\delta = 3.39$ , showed a cross peak to  $\text{H}^g$ ,  $\text{H}^i$  &  $\text{H}^j$   
 $\text{H}^i$ ,  $\delta = 4.57$ , showed a cross peak to  $\text{H}^h$  &  $\text{CH}_3$   
 $\text{H}^j$ ,  $\delta = 5.04$ , showed a cross peak to  $\text{H}^g$ ,  $\text{H}^h$  & aromatic H  
 at  $\delta = 7.22 - 7.15$   
 $\text{CH}_3$ ,  $\delta = 0.99$  showed a cross peak to  $\text{H}^i$

**[(1*RS*,2*RS*,4*SR*,5*RS*,9*RS*)-9-Chloro-2-methyl-4-phenyl-3-oxa-bicyclo[3.3.1]non-7-en-1-yl]-methanol (321)**: Colourless crystalline solid (70 mg, 25 %), m.p. 144 – 145 °C;  $\nu_{\text{max}}$  ( $\text{CH}_2\text{Cl}_2$ )/ $\text{cm}^{-1}$  3429 (broad), 3030, 2924, 1653, 1451, 1387, 1368, 1310, 1250, 1119, 1058, 1031, 724;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.31 – 7.16 (5 H, m, 5  $\times$  aromatic CH), 5.87 (1 H, app. dt,  $J$  10.0, 3.4,  $\text{H}^b$ ), 5.06 (1 H, app. dq,  $J$  10.0, 1.9,  $\text{H}^a$ ), 4.70 (2 H, broad resonance,  $\text{H}^h$  and  $\text{H}^f$ ), 3.96 (1 H, d,  $J$  11.2,  $\text{H}^i$ ), 3.90 (1 H, q,  $J$  6.2,  $\text{H}^e$ ), 3.64 (1 H, d,  $J$  11.2,  $\text{H}^j$ ), 2.42 – 2.36 (1 H, m, ring junction  $\text{H}^c$ ), 2.90 (1 H, app. ddt,  $J$  19.3, 6.7, 2.7,  $\text{H}^g$ ), 1.87 – 1.78 (1 H, m,  $\text{H}^d$ ), 1.20 (3 H, d,  $J$  6.2,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 140.2 (aromatic  $\text{C}_q$ ), 130.9 (alkene CH), 128.2 (2  $\times$  *o*-aromatic CH), 127.2 (*p*-aromatic CH), 125.6 (2  $\times$  *m*-aromatic CH), 121.5 (alkene), 81.7 (O-CH-Ph), 77.1 (O-CH-CH<sub>3</sub>), 63.6 (O-CH<sub>2</sub>), 63.1 (CH-Cl), 46.6 (ring  $\text{C}_q$ ), 41.9 (O-CH-CH<sub>2</sub>), 23.2 (ring CH<sub>2</sub>), 16.3 ( $\text{CH}_3$ ).

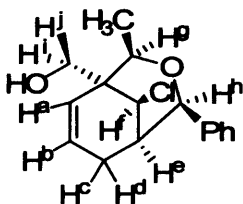
$^1\text{H} - ^1\text{H}$  COSY experiment showed the following correlations



321

$\text{H}^a$ ,  $\delta = 5.06$ , showed a cross peak to  $\text{H}^b$ ,  $\text{H}^c$  &  $\text{H}^d$   
 $\text{H}^b$ ,  $\delta = 5.87$ , showed a cross peak to  $\text{H}^a$  &  $\text{H}^d$   
 $\text{H}^c$ ,  $\delta = 2.09$ , showed a cross peak to  $\text{H}^a$ ,  $\text{H}^d$  &  $\text{H}^e$   
 $\text{H}^d$ ,  $\delta = 1.87 - 1.78$ , showed a cross peak to  $\text{H}^a$ ,  $\text{H}^b$  &  $\text{H}^c$   
 $\text{H}^e$ ,  $\delta = 2.42 - 2.36$ , showed a cross peak to  $\text{H}^c$ ,  $\text{H}^h$  &  $\text{H}^f$   
 $\text{H}^f$  &  $\text{H}^h$ ,  $\delta = 4.70$ , showed a cross peak to  $\text{H}^e$   
 $\text{H}^g$ ,  $\delta = 3.90$ , showed a cross peak to  $\text{CH}_3$   
 $\text{H}^i$ ,  $\delta = 3.96$ , showed a cross peak to  $\text{H}^j$   
 $\text{H}^j$ ,  $\delta = 3.64$ , showed a cross peak to  $\text{H}^i$   
 $\text{CH}_3$ ,  $\delta = 1.20$ , showed a cross peak to  $\text{H}^g$

NOESY experiment showed the following correlations



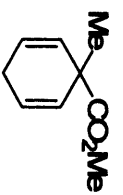
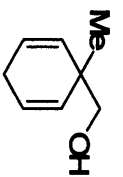
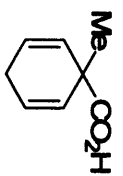
321

$\text{H}^a$ ,  $\delta = 5.06$  showed, a cross peak to  $\text{H}^b$ ,  $\text{H}^c$ ,  $\text{H}^d$ ,  $\text{H}^j$ ,  $\text{H}^i$  &  $\text{CH}_3$   
 $\text{H}^b$ ,  $\delta = 5.87$ , showed a cross peak to  $\text{H}^a$ ,  $\text{H}^c$  &  $\text{H}^d$   
 $\text{H}^c$ ,  $\delta = 2.09$ , showed a cross peak to  $\text{H}^a$ ,  $\text{H}^b$ ,  $\text{H}^d$  &  $\text{H}^e$   
 $\text{H}^d$ ,  $\delta = 1.87 - 1.78$ , showed a cross peak to  $\text{H}^a$ ,  $\text{H}^b$ ,  $\text{H}^c$  &  $\text{H}^e$   
 $\text{H}^e$ ,  $\delta = 2.42 - 2.36$ , showed a cross peak to aromatic protons,  $\text{H}^c$ ,  $\text{H}^d$ ,  $\text{H}^h$  &  $\text{H}^f$   
 $\text{H}^f$  &  $\text{H}^h$ ,  $\delta = 4.70$ , showed a cross peak to aromatic protons,  $\text{H}^e$  &  $\text{H}^g$   
 $\text{H}^g$ ,  $\delta = 3.90$ , showed a cross peak to  $\text{CH}_3$ ,  $\text{H}^h$  &  $\text{H}^f$   
 $\text{H}^i$ ,  $\delta = 3.96$ , showed a cross peak to  $\text{H}^j$ ,  $\text{H}^a$  &  $\text{OH}$   
 $\text{H}^j$ ,  $\delta = 3.64$ , showed a cross peak to  $\text{H}^i$ ,  $\text{H}^a$  &  $\text{CH}_3$   
 $\text{CH}_3$ ,  $\delta = 1.20$ , showed a cross peak to  $\text{H}^g$ ,  $\text{H}^a$  &  $\text{H}^j$



## **Appendix A**

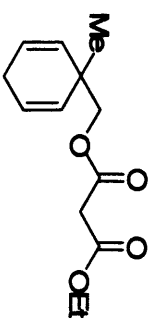
### **Compound List**



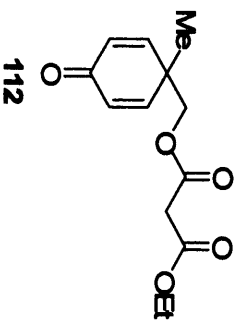
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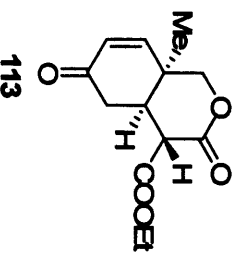
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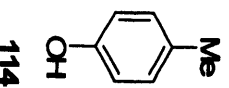
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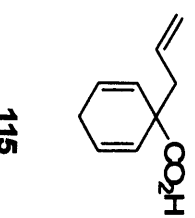
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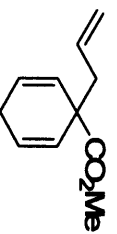
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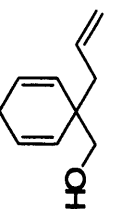
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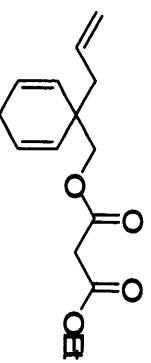
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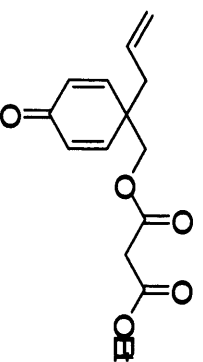
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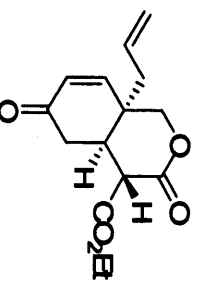
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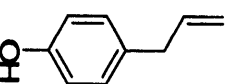
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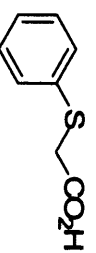
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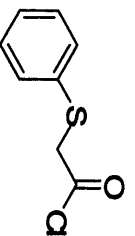
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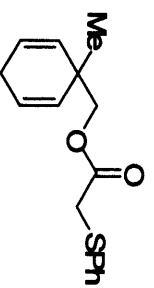
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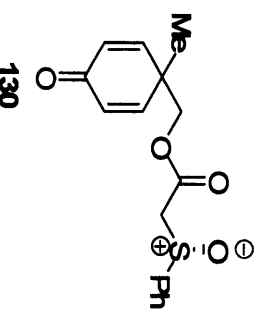
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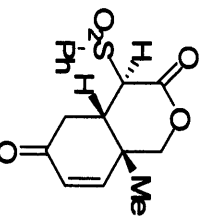
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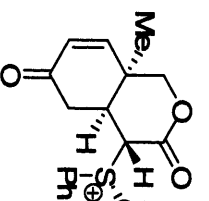
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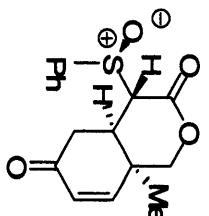
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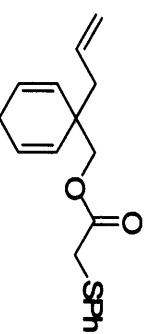
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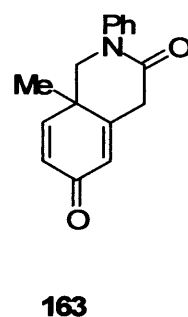
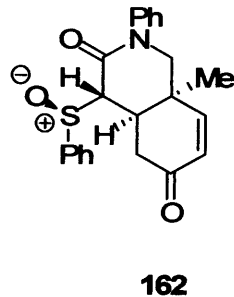
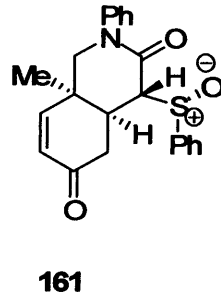
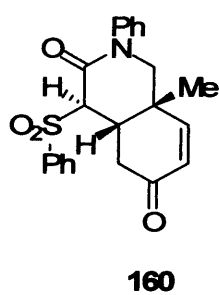
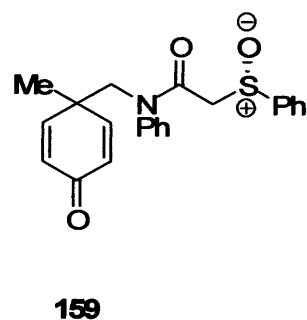
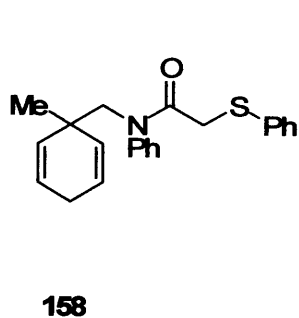
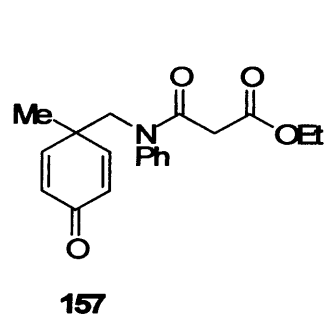
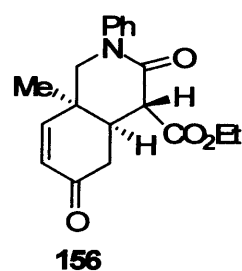
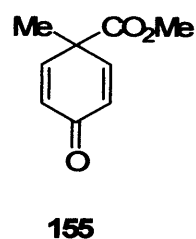
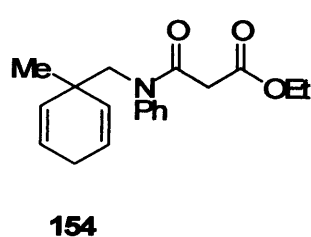
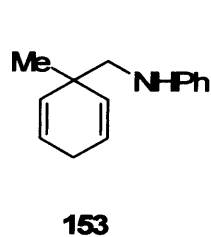
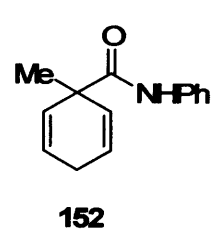
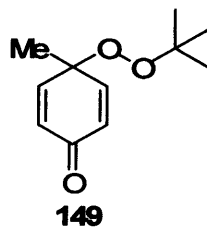
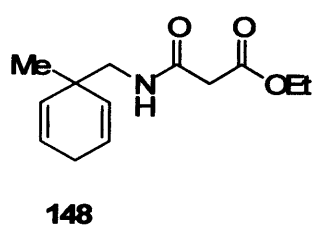
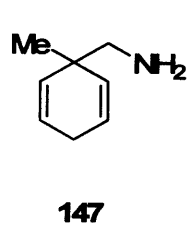
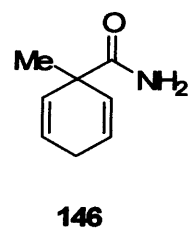
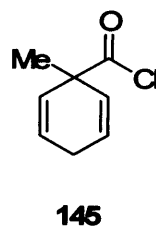
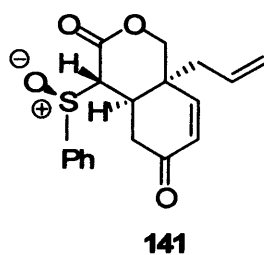
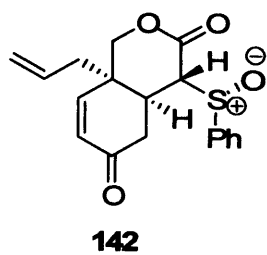
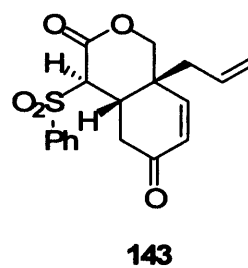
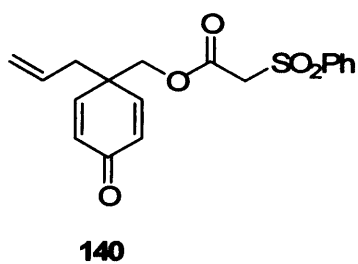
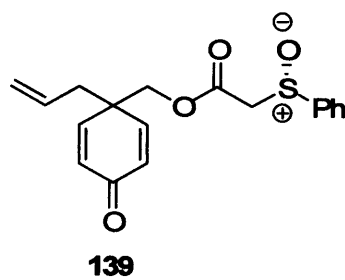
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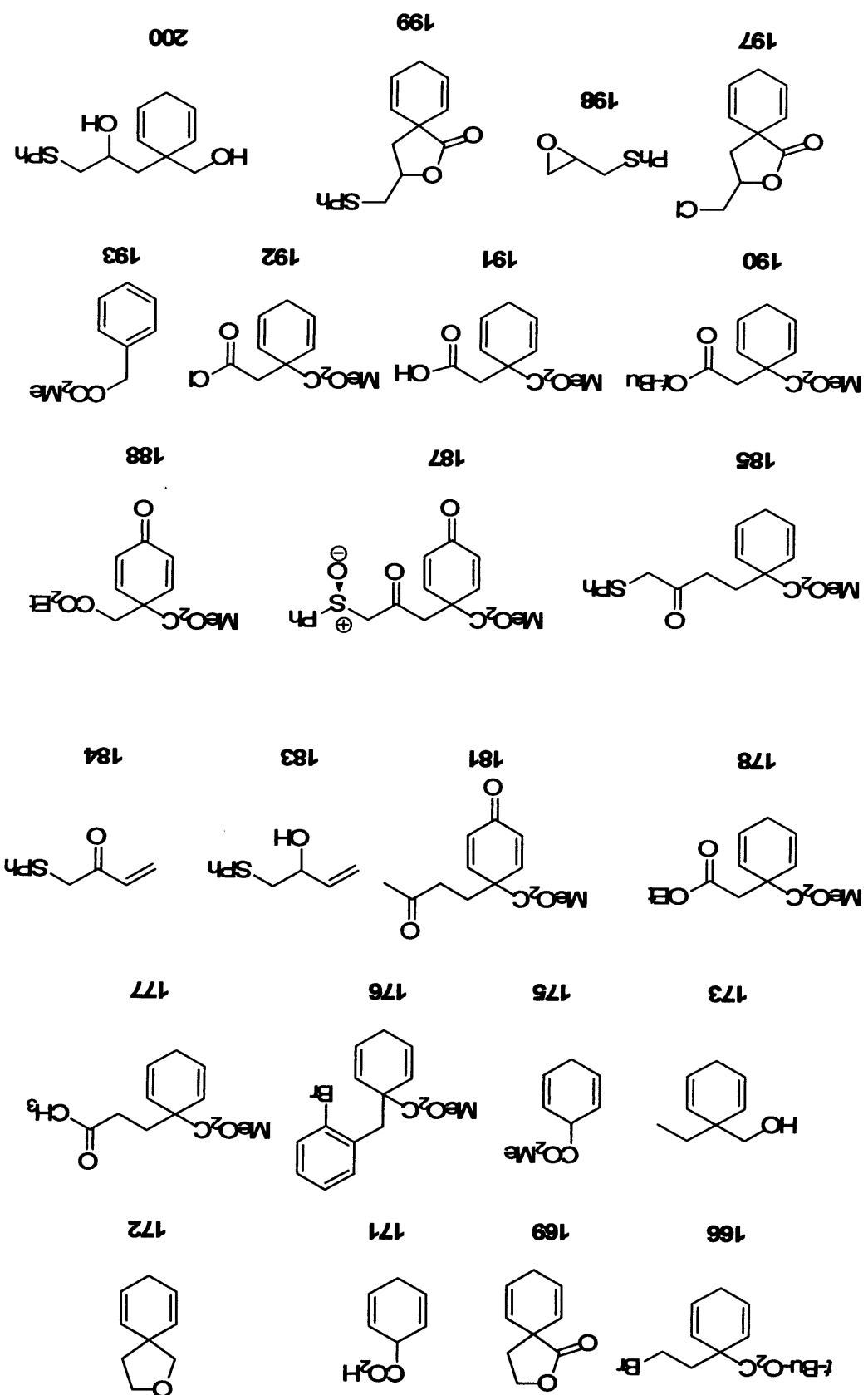


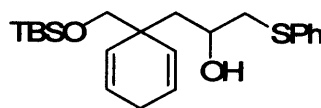
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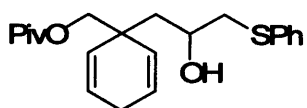
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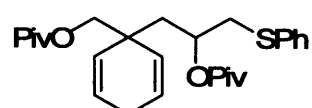




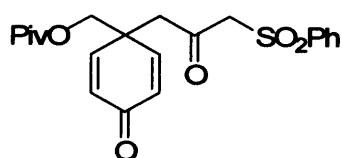
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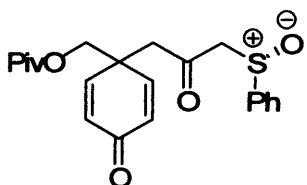
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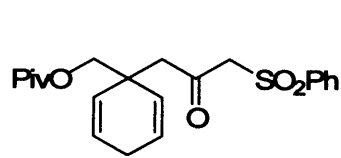
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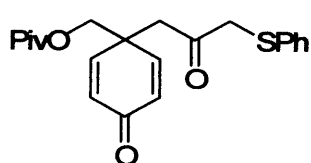
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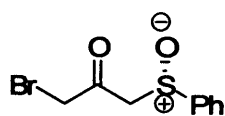
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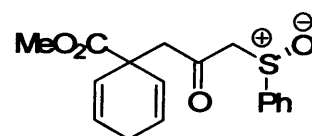
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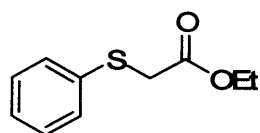
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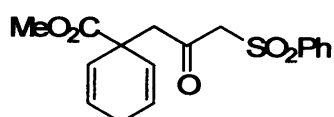
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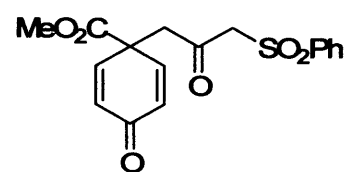
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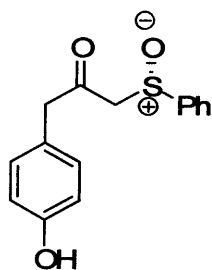
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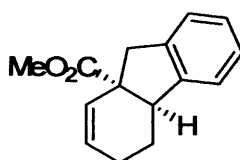
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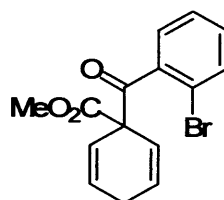
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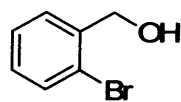
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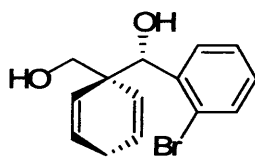
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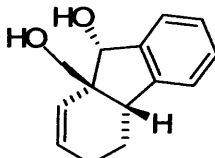
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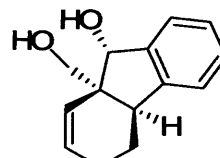
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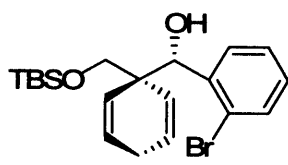
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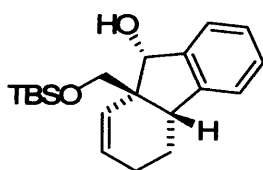
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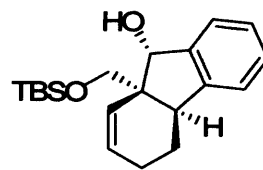
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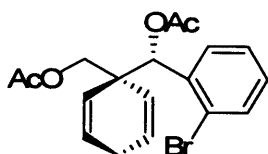
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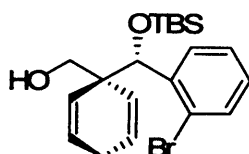
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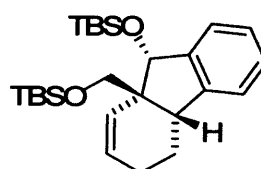
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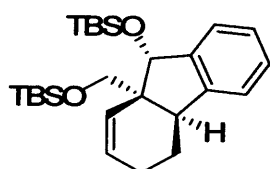
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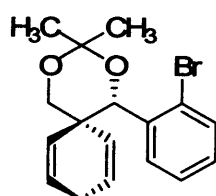
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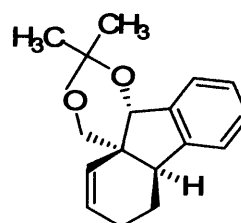
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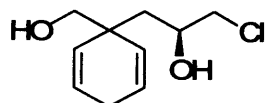
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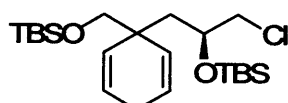
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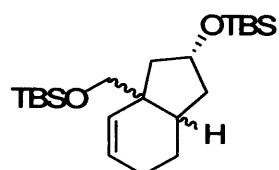
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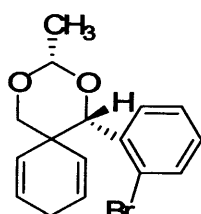
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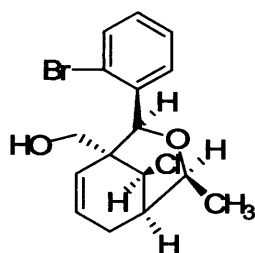
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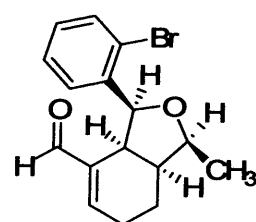
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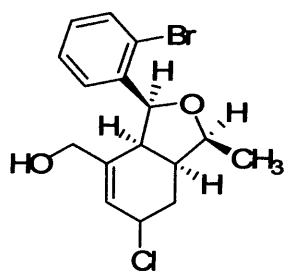
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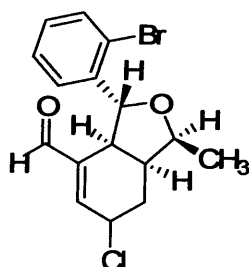
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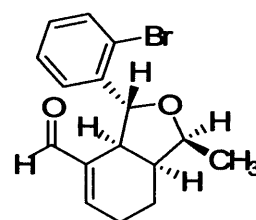
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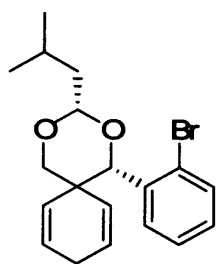
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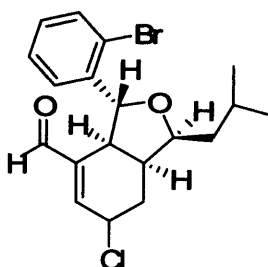
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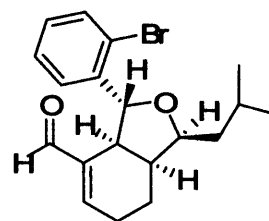
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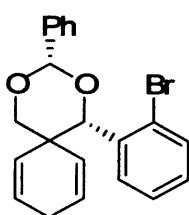
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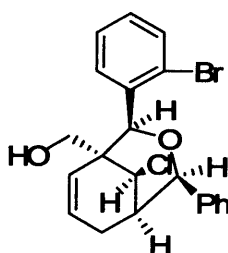
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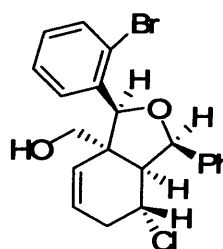
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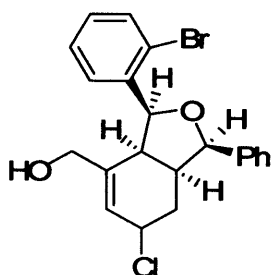
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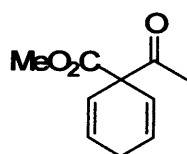
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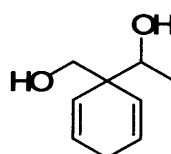
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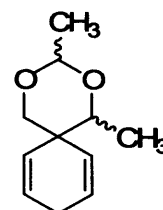
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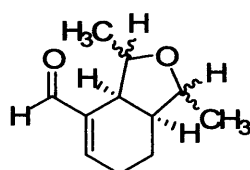
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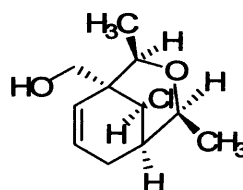
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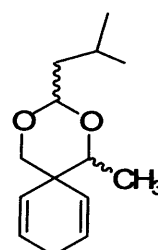
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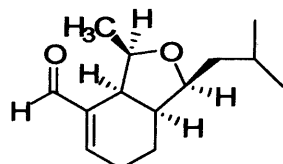
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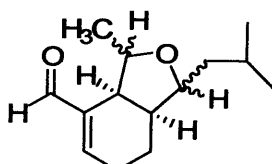
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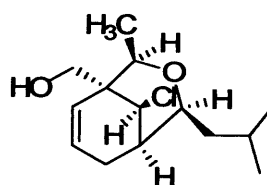
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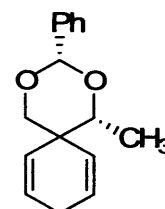
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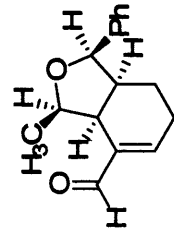
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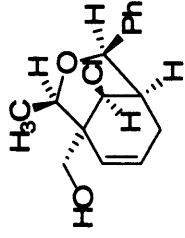
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319



320



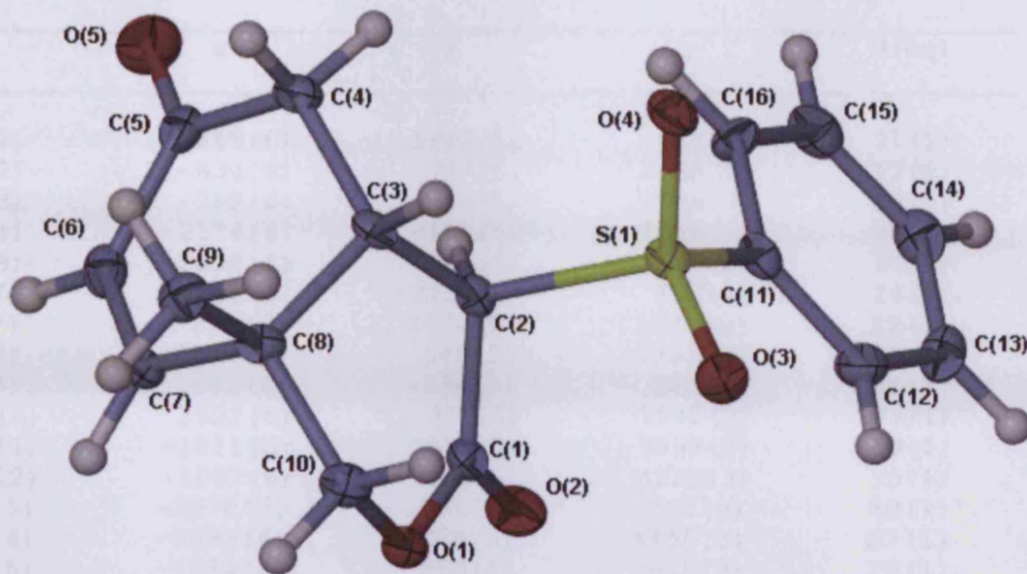
321



## **Appendix B**

### **Crystallographic Data**

Table 1. Crystal data and structure refinement for compound **132**.



Empirical formula	C <sub>16</sub> H <sub>16</sub> O <sub>5</sub> S
Formula weight	320.35
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P 2 <sub>1</sub> /n
Unit cell dimensions	a = 7.6838(3) Å, α = 90° b = 9.4701(4) Å, β = 100.667(2)° c = 20.2770(11) Å, γ = 90°
Volume	1449.99(11) Å <sup>3</sup>
Z, Calculated density	4, 1.467 Mg/m <sup>3</sup>
Absorption coefficient	0.245 mm <sup>-1</sup>
F(000)	672
Crystal size	0.20 x 0.20 x 0.20 mm
Theta range for data collection	2.97 to 27.51 °
Limiting indices	-9 ≤ h ≤ 9, -10 ≤ k ≤ 12, -20 ≤ l ≤ 26
Reflections collected / unique	8584 / 3275 [R(int) = 0.0941]
Completeness to theta = 27.51	98.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9526 and 0.9526
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	3275 / 0 / 199
Goodness-of-fit on F <sup>2</sup>	1.079
Final R indices [I > 2σ(I)]	R <sub>1</sub> = 0.0816, wR <sub>2</sub> = 0.1771
R indices (all data)	R <sub>1</sub> = 0.1309, wR <sub>2</sub> = 0.1949
Largest diff. peak and hole	0.518 and -0.642 e.Å <sup>-3</sup>

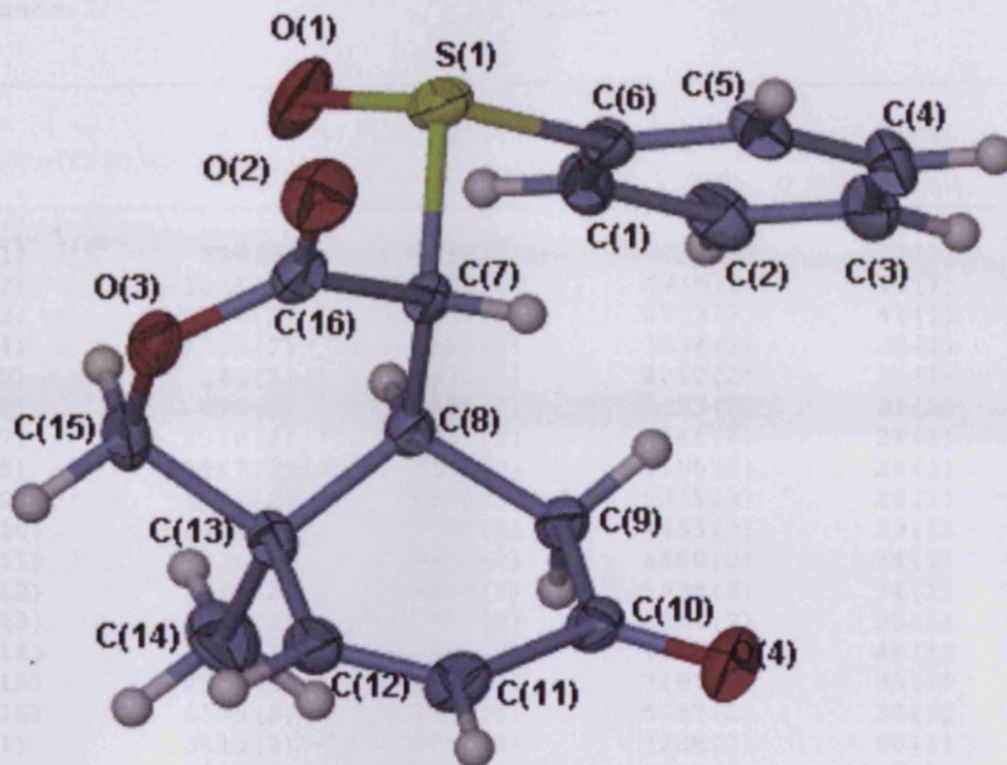
Table 2. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for compound **132**. U(eq) is defined as one third of the trace of the orthogonalised  $U_{ij}$  tensor.

	x	y	z	U(eq)
C(1)	648(6)	1942(5)	2618(2)	21(1)
C(2)	-630(6)	747(5)	2368(2)	17(1)
C(3)	-382(6)	-81(5)	1726(2)	18(1)
C(4)	-2174(6)	-188(5)	1245(2)	23(1)
C(5)	-2802(6)	1207(5)	925(2)	24(1)
C(6)	-1422(6)	2228(5)	830(2)	24(1)
C(7)	291(6)	1974(5)	1043(2)	22(1)
C(8)	1030(6)	640(5)	1393(2)	20(1)
C(9)	1682(6)	-334(5)	883(2)	24(1)
C(10)	2622(6)	971(5)	1942(2)	23(1)
C(11)	-1811(6)	326(5)	3596(2)	19(1)
C(12)	-1007(6)	843(5)	4220(3)	25(1)
C(13)	-2078(7)	1356(5)	4652(3)	28(1)
C(14)	-3893(6)	1368(5)	4450(3)	27(1)
C(15)	-4684(6)	889(5)	3820(3)	28(1)
C(16)	-3645(6)	354(5)	3387(2)	22(1)
O(1)	2197(4)	2023(3)	2406(2)	23(1)
O(2)	297(5)	2815(4)	3006(2)	31(1)
O(3)	1297(4)	-539(4)	3412(2)	26(1)
O(4)	-1395(4)	-1751(3)	2802(2)	25(1)
O(5)	-4366(4)	1482(4)	742(2)	37(1)
S(1)	-517(2)	-470(1)	3067(1)	19(1)

Table 3. Bond lengths [Å] and angles [°] for compound **132**.

C(1)-O(2)	1.204(6)	C(5)-C(4)-H(4A)	109.0
C(1)-O(1)	1.341(5)	C(3)-C(4)-H(4A)	109.0
C(1)-C(2)	1.523(6)	C(5)-C(4)-H(4B)	109.0
C(2)-C(3)	1.561(6)	C(3)-C(4)-H(4B)	109.0
C(2)-S(1)	1.817(4)	H(4A)-C(4)-H(4B)	107.8
C(2)-H(2)	1.0000	O(5)-C(5)-C(6)	120.9(5)
C(3)-C(4)	1.536(6)	O(5)-C(5)-C(4)	122.4(5)
C(3)-C(8)	1.539(6)	C(6)-C(5)-C(4)	116.7(4)
C(3)-H(3)	1.0000	C(7)-C(6)-C(5)	122.2(5)
C(4)-C(5)	1.511(7)	C(7)-C(6)-H(6)	118.9
C(4)-H(4A)	0.9900	C(5)-C(6)-H(6)	118.9
C(4)-H(4B)	0.9900	C(6)-C(7)-C(8)	124.6(4)
C(5)-O(5)	1.218(6)	C(6)-C(7)-H(7)	117.7
C(5)-C(6)	1.473(7)	C(8)-C(7)-H(7)	117.7
C(6)-C(7)	1.330(7)	C(7)-C(8)-C(10)	110.6(4)
C(6)-H(6)	0.9500	C(7)-C(8)-C(9)	109.1(4)
C(7)-C(8)	1.508(7)	C(10)-C(8)-C(9)	107.3(4)
C(7)-H(7)	0.9500	C(7)-C(8)-C(3)	110.1(4)
C(8)-C(10)	1.526(6)	C(10)-C(8)-C(3)	107.8(4)
C(8)-C(9)	1.537(6)	C(9)-C(8)-C(3)	111.8(4)
C(9)-H(9A)	0.9800	C(8)-C(9)-H(9A)	109.5
C(9)-H(9B)	0.9800	C(8)-C(9)-H(9B)	109.5
C(9)-H(9C)	0.9800	H(9A)-C(9)-H(9B)	109.5
C(10)-O(1)	1.449(6)	C(8)-C(9)-H(9C)	109.5
C(10)-H(10A)	0.9900	H(9A)-C(9)-H(9C)	109.5
C(10)-H(10B)	0.9900	H(9B)-C(9)-H(9C)	109.5
C(11)-C(12)	1.390(7)	O(1)-C(10)-C(8)	111.6(4)
C(11)-C(16)	1.395(6)	O(1)-C(10)-H(10A)	109.3
C(11)-S(1)	1.761(4)	C(8)-C(10)-H(10A)	109.3
C(12)-C(13)	1.395(7)	O(1)-C(10)-H(10B)	109.3
C(12)-H(12)	0.9500	C(8)-C(10)-H(10B)	109.3
C(13)-C(14)	1.379(7)	H(10A)-C(10)-H(10B)	108.0
C(13)-H(13)	0.9500	C(12)-C(11)-C(16)	121.6(4)
C(14)-C(15)	1.385(7)	C(12)-C(11)-S(1)	119.9(4)
C(14)-H(14)	0.9500	C(16)-C(11)-S(1)	118.4(4)
C(15)-C(16)	1.388(6)	C(11)-C(12)-C(13)	118.6(4)
C(15)-H(15)	0.9500	C(11)-C(12)-H(12)	120.7
C(16)-H(16)	0.9500	C(13)-C(12)-H(12)	120.7
O(3)-S(1)	1.440(3)	C(14)-C(13)-C(12)	119.9(5)
O(4)-S(1)	1.442(3)	C(14)-C(13)-H(13)	120.0
		C(12)-C(13)-H(13)	120.0
O(2)-C(1)-O(1)	119.3(4)	C(13)-C(14)-C(15)	121.2(5)
O(2)-C(1)-C(2)	121.3(4)	C(13)-C(14)-H(14)	119.4
O(1)-C(1)-C(2)	119.4(4)	C(15)-C(14)-H(14)	119.4
C(1)-C(2)-C(3)	118.7(4)	C(14)-C(15)-C(16)	119.8(4)
C(1)-C(2)-S(1)	106.1(3)	C(14)-C(15)-H(15)	120.1
C(3)-C(2)-S(1)	109.7(3)	C(16)-C(15)-H(15)	120.1
C(1)-C(2)-H(2)	107.3	C(15)-C(16)-C(11)	118.8(4)
C(3)-C(2)-H(2)	107.3	C(15)-C(16)-H(16)	120.6
S(1)-C(2)-H(2)	107.3	C(11)-C(16)-H(16)	120.6
C(4)-C(3)-C(8)	111.9(4)	C(1)-O(1)-C(10)	119.3(4)
C(4)-C(3)-C(2)	109.2(4)	O(3)-S(1)-O(4)	119.1(2)
C(8)-C(3)-C(2)	110.3(4)	O(3)-S(1)-C(11)	109.2(2)
C(4)-C(3)-H(3)	108.4	O(4)-S(1)-C(11)	108.0(2)
C(8)-C(3)-H(3)	108.4	O(3)-S(1)-C(2)	108.0(2)
C(2)-C(3)-H(3)	108.4	O(4)-S(1)-C(2)	107.0(2)
C(5)-C(4)-C(3)	113.1(4)	C(11)-S(1)-C(2)	104.6(2)

Table 1. Crystal data and structure refinement for compound **133**.



Empirical formula	C <sub>16</sub> H <sub>16</sub> O <sub>4</sub> S
Formula weight	304.35
Temperature	180(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P 2 <sub>1</sub> /c
Unit cell dimensions	a = 10.8528(3) Å, α = 90° b = 12.0026(3) Å, β = 109.4890(10)° c = 11.7968(3) Å, γ = 90°
Volume	1448.63(7) Å <sup>3</sup>
Z, Calculated density	4, 1.395 Mg/m <sup>3</sup>
Absorption coefficient	0.236 mm <sup>-1</sup>
F(000)	640
Crystal size	0.25 x 0.20 x 0.10 mm
Theta range for data collection	3.39 to 29.99°
Limiting indices	-15 ≤ h ≤ 15, -16 ≤ k ≤ 16, -16 ≤ l ≤ 16
Reflections collected / unique	26398 / 4208 [R(int) = 0.1258]
Completeness to theta = 29.99	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9768 and 0.9433
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	4208 / 0 / 191
Goodness-of-fit on F <sup>2</sup>	1.033
Final R indices [I > 2σ(I)]	R <sub>1</sub> = 0.0591, wR <sub>2</sub> = 0.1313
R indices (all data)	R <sub>1</sub> = 0.0964, wR <sub>2</sub> = 0.1471
Largest diff. peak and hole	0.298 and -0.620 e.Å <sup>-3</sup>

Table 2. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for compound **133**. U(eq) is defined as one third of the trace of the orthogonalised  $U_{ij}$  tensor.

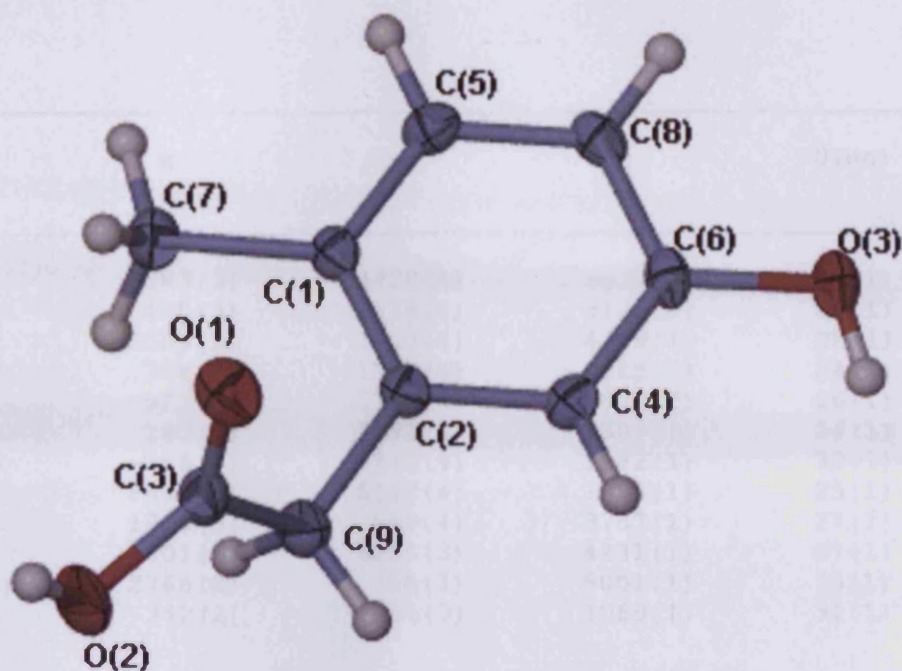
	x	y	z	U(eq)
C(1)	308(2)	3297(2)	6338(2)	37(1)
C(2)	-1035(2)	3136(2)	5969(2)	40(1)
C(3)	-1774(2)	3233(2)	4773(2)	41(1)
C(4)	-1196(2)	3510(2)	3934(2)	39(1)
C(5)	140(2)	3670(2)	4282(2)	35(1)
C(6)	886(2)	3538(2)	5493(2)	31(1)
C(7)	3046(2)	2315(2)	5546(2)	28(1)
C(8)	2547(2)	1398(2)	6195(2)	25(1)
C(9)	1362(2)	800(2)	5318(2)	28(1)
C(10)	1720(2)	48(2)	4453(2)	29(1)
C(11)	3036(2)	-438(2)	4860(2)	34(1)
C(12)	3897(2)	-218(2)	5938(2)	34(1)
C(13)	3629(2)	563(2)	6834(2)	28(1)
C(14)	3257(2)	-113(2)	7780(2)	48(1)
C(15)	4852(2)	1231(2)	7497(2)	35(1)
C(16)	4505(2)	2388(2)	5757(2)	30(1)
O(1)	3115(2)	3751(2)	7288(2)	66(1)
O(2)	4923(2)	2926(1)	5108(1)	45(1)
O(3)	5342(1)	1854(1)	6689(1)	<b>34(1)</b>
O(4)	914(1)	-197(1)	3478(1)	<b>40(1)</b>
S(1)	2620(1)	3728(1)	5950(1)	<b>47(1)</b>

Table 3. Bond lengths [Å] and angles [°] for compound **133**.

C(1)-C(6)	1.374(3)	C(1)-C(6)-C(5)	121.15(18)
C(1)-C(2)	1.388(3)	C(1)-C(6)-S(1)	119.75(15)
C(1)-H(1)	0.9500	C(5)-C(6)-S(1)	119.07(17)
C(2)-C(3)	1.376(3)	C(16)-C(7)-C(8)	118.67(15)
C(2)-H(2)	0.9500	C(16)-C(7)-S(1)	103.83(12)
C(3)-C(4)	1.378(3)	C(8)-C(7)-S(1)	111.47(13)
C(3)-H(3)	0.9500	C(16)-C(7)-H(7)	107.4
C(4)-C(5)	1.383(3)	C(8)-C(7)-H(7)	107.4
C(4)-H(4)	0.9500	S(1)-C(7)-H(7)	107.4
C(5)-C(6)	1.396(3)	C(9)-C(8)-C(13)	110.94(15)
C(5)-H(5)	0.9500	C(9)-C(8)-C(7)	110.74(15)
C(6)-S(1)	1.7911(19)	C(13)-C(8)-C(7)	111.85(14)
C(7)-C(16)	1.521(3)	C(9)-C(8)-H(8)	107.7
C(7)-C(8)	1.539(3)	C(13)-C(8)-H(8)	107.7
C(7)-S(1)	1.8616(19)	C(7)-C(8)-H(8)	107.7
C(7)-H(7)	1.0000	C(10)-C(9)-C(8)	112.94(15)
C(8)-C(9)	1.533(2)	C(10)-C(9)-H(9A)	109.0
C(8)-C(13)	1.536(2)	C(8)-C(9)-H(9A)	109.0
C(8)-H(8)	1.0000	C(10)-C(9)-H(9B)	109.0
C(9)-C(10)	1.507(3)	C(8)-C(9)-H(9B)	109.0
C(9)-H(9A)	0.9900	H(9A)-C(9)-H(9B)	107.8
C(9)-H(9B)	0.9900	O(4)-C(10)-C(11)	121.55(19)
C(10)-O(4)	1.226(2)	O(4)-C(10)-C(9)	121.00(17)
C(10)-C(11)	1.467(3)	C(11)-C(10)-C(9)	117.31(16)
C(11)-C(12)	1.330(3)	C(12)-C(11)-C(10)	122.07(18)
C(11)-H(11)	0.9500	C(12)-C(11)-H(11)	119.0
C(12)-C(13)	1.511(3)	C(10)-C(11)-H(11)	119.0
C(12)-H(12)	0.9500	C(11)-C(12)-C(13)	123.65(17)
C(13)-C(15)	1.524(3)	C(11)-C(12)-H(12)	118.2
C(13)-C(14)	1.538(3)	C(13)-C(12)-H(12)	118.2
C(14)-H(14A)	0.9800	C(12)-C(13)-C(15)	110.32(16)
C(14)-H(14B)	0.9800	C(12)-C(13)-C(8)	110.82(15)
C(14)-H(14C)	0.9800	C(15)-C(13)-C(8)	107.53(16)
C(15)-O(3)	1.445(2)	C(12)-C(13)-C(14)	109.78(17)
C(15)-H(15A)	0.9900	C(15)-C(13)-C(14)	107.42(16)
C(15)-H(15B)	0.9900	C(8)-C(13)-C(14)	110.89(16)
C(16)-O(2)	1.200(2)	C(13)-C(14)-H(14A)	109.5
C(16)-O(3)	1.334(2)	C(13)-C(14)-H(14B)	109.5
O(1)-S(1)	1.488(2)	H(14A)-C(14)-H(14B)	109.5
		C(13)-C(14)-H(14C)	109.5
C(6)-C(1)-C(2)	119.15(18)	H(14A)-C(14)-H(14C)	109.5
C(6)-C(1)-H(1)	120.4	H(14B)-C(14)-H(14C)	109.5
C(2)-C(1)-H(1)	120.4	O(3)-C(15)-C(13)	112.49(15)
C(3)-C(2)-C(1)	120.1(2)	O(3)-C(15)-H(15A)	109.1
C(3)-C(2)-H(2)	119.9	C(13)-C(15)-H(15A)	109.1
C(1)-C(2)-H(2)	119.9	O(3)-C(15)-H(15B)	109.1
C(2)-C(3)-C(4)	120.5(2)	C(13)-C(15)-H(15B)	109.1
C(2)-C(3)-H(3)	119.7	H(15A)-C(15)-H(15B)	107.8
C(4)-C(3)-H(3)	119.7	O(2)-C(16)-O(3)	119.09(18)
C(3)-C(4)-C(5)	120.25(19)	O(2)-C(16)-C(7)	121.42(18)
C(3)-C(4)-H(4)	119.9	O(3)-C(16)-C(7)	119.49(17)
C(5)-C(4)-H(4)	119.9	C(16)-O(3)-C(15)	119.58(14)
C(4)-C(5)-C(6)	118.8(2)	O(1)-S(1)-C(6)	107.04(11)
C(4)-C(5)-H(5)	120.6	O(1)-S(1)-C(7)	104.78(9)
C(6)-C(5)-H(5)	120.6	C(6)-S(1)-C(7)	97.61(8)



Table 1. Crystal data and structure refinement for compound **134**.



Empirical formula	C <sub>9</sub> H <sub>10</sub> O <sub>3</sub>
Formula weight	166.17
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P 2 <sub>1</sub> /n
Unit cell dimensions	a = 7.5260(3) Å, α = 90.000(2)° b = 5.9400(3) Å, β = 99.857(2)° c = 18.1810(9) Å, γ = 90.000(2)°
Volume	800.77(7) Å <sup>3</sup>
Z, Calculated density	4, 1.378 Mg/m <sup>3</sup>
Absorption coefficient	0.104 mm <sup>-1</sup>
F(000)	352
Crystal size	0.25 x 0.08 x 0.05 mm
Theta range for data collection	3.15 to 27.55°
Limiting indices	-9 ≤ h ≤ 9, -7 ≤ k ≤ 7, -23 ≤ l ≤ 19
Reflections collected / unique	9358 / 1826 [R(int) = 0.1204]
Completeness to theta = 27.55	98.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9948 and 0.9746
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	1826 / 0 / 112
Goodness-of-fit on F <sup>2</sup>	1.028
Final R indices [I > 2σ(I)]	R <sub>1</sub> = 0.0616, wR <sub>2</sub> = 0.1223
R indices (all data)	R <sub>1</sub> = 0.1067, wR <sub>2</sub> = 0.1439
Largest diff. peak and hole	0.236 and -0.327 e.Å <sup>-3</sup>



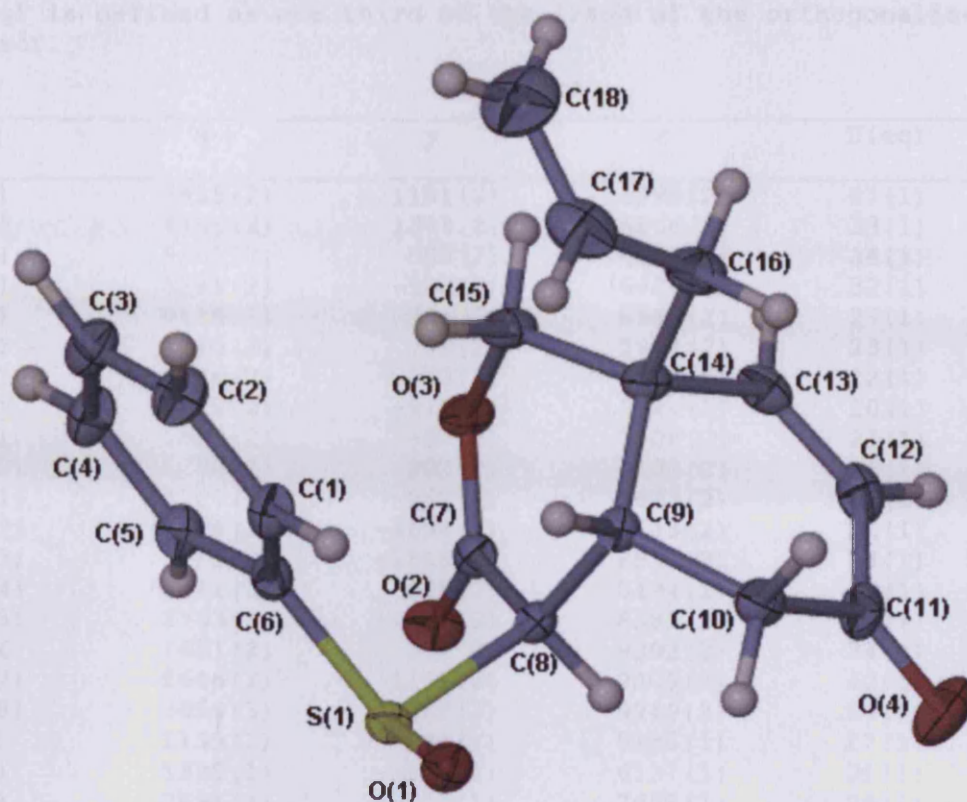
Table 2. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for compound **134**  
 $U(\text{eq})$  is defined as one third of the trace of the orthogonalised  $U_{ij}$  tensor.

	x	y	z	$U(\text{eq})$
C(1)	-383(3)	4428(4)	3227(1)	23(1)
C(2)	470(3)	2378(4)	3126(1)	22(1)
C(3)	2605(3)	1803(4)	4349(1)	28(1)
C(4)	734(3)	1727(4)	2415(1)	24(1)
C(5)	-923(3)	5781(4)	2607(1)	26(1)
C(6)	143(3)	3091(4)	1809(1)	24(1)
C(7)	-754(3)	5141(4)	3982(1)	32(1)
C(8)	-672(3)	5142(4)	1898(1)	25(1)
C(9)	1073(3)	859(4)	3787(1)	27(1)
O(1)	3601(2)	3290(3)	4231(1)	37(1)
O(2)	2766(2)	746(3)	5001(1)	36(1)
O(3)	342(2)	2504(3)	1089(1)	31(1)

Table 3. Bond lengths [Å] and angles [°] for compound **134**.

C(1)-C(5)	1.387(3)	O(1)-C(3)-O(2)	122.9(2)
C(1)-C(2)	1.403(3)	O(1)-C(3)-C(9)	125.4(2)
C(1)-C(7)	1.509(3)	O(2)-C(3)-C(9)	111.7(2)
C(2)-C(4)	1.396(3)	C(6)-C(4)-C(2)	120.0(2)
C(2)-C(9)	1.508(3)	C(6)-C(4)-H(4)	120.0
C(3)-O(1)	1.201(3)	C(2)-C(4)-H(4)	120.0
C(3)-O(2)	1.329(3)	C(1)-C(5)-C(8)	121.9(2)
C(3)-C(9)	1.512(3)	C(1)-C(5)-H(5)	119.0
C(4)-C(6)	1.379(3)	C(8)-C(5)-H(5)	119.0
C(4)-H(4)	0.9500	C(4)-C(6)-C(8)	120.8(2)
C(5)-C(8)	1.389(3)	C(4)-C(6)-O(3)	122.3(2)
C(5)-H(5)	0.9500	C(8)-C(6)-O(3)	116.88(19)
C(6)-C(8)	1.385(3)	C(1)-C(7)-H(7A)	109.5
C(6)-O(3)	1.387(2)	C(1)-C(7)-H(7B)	109.5
C(7)-H(7A)	0.9800	H(7A)-C(7)-H(7B)	109.5
C(7)-H(7B)	0.9800	C(1)-C(7)-H(7C)	109.5
C(7)-H(7C)	0.9800	H(7A)-C(7)-H(7C)	109.5
C(8)-H(8)	0.9500	H(7B)-C(7)-H(7C)	109.5
C(9)-H(9A)	0.9900	C(6)-C(8)-C(5)	118.8(2)
C(9)-H(9B)	0.9900	C(6)-C(8)-H(8)	120.6
O(2)-H(2)	0.8400	C(5)-C(8)-H(8)	120.6
O(3)-H(3)	0.8400	C(2)-C(9)-C(3)	114.00(19)
		C(2)-C(9)-H(9A)	108.8
C(5)-C(1)-C(2)	118.3(2)	C(3)-C(9)-H(9A)	108.8
C(5)-C(1)-C(7)	120.2(2)	C(2)-C(9)-H(9B)	108.8
C(2)-C(1)-C(7)	121.5(2)	C(3)-C(9)-H(9B)	108.8
C(4)-C(2)-C(1)	120.1(2)	H(9A)-C(9)-H(9B)	107.6
C(4)-C(2)-C(9)	120.0(2)	C(3)-O(2)-H(2)	109.5
C(1)-C(2)-C(9)	119.85(19)	C(6)-O(3)-H(3)	109.5

Table 1. Crystal data and structure refinement for compound **141**.



Empirical formula	C <sub>18</sub> H <sub>18</sub> O <sub>4</sub> S
Formula weight	330.38
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P 2 <sub>1</sub> /c
Unit cell dimensions	a = 11.2302(3) Å, α = 90° b = 11.2665(4) Å, β = 95.6720(10)° c = 12.7755(5) Å, γ = 90°
Volume	1608.51(10) Å <sup>3</sup>
Z, Calculated density	4, 1.364 Mg/m <sup>3</sup>
Absorption coefficient	0.219 mm <sup>-1</sup>
F(000)	696
Crystal size	0.23 x 0.15 x 0.15 mm
Theta range for data collection	2.93 to 27.48°
Limiting indices	-13 ≤ h ≤ 12, -14 ≤ k ≤ 14, -16 ≤ l ≤ 16
Reflections collected / unique	10072 / 3380 [R(int) = 0.0543]
Completeness to theta = 27.48	91.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9679 and 0.9514
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	3380 / 0 / 208
Goodness-of-fit on F <sup>2</sup>	1.058
Final R indices [I > 2σ(I)]	R <sub>1</sub> = 0.0501, wR <sub>2</sub> = 0.1060
R indices (all data)	R <sub>1</sub> = 0.0725, wR <sub>2</sub> = 0.1147
Largest diff. peak and hole	0.456 and -0.383 e.Å <sup>-3</sup>

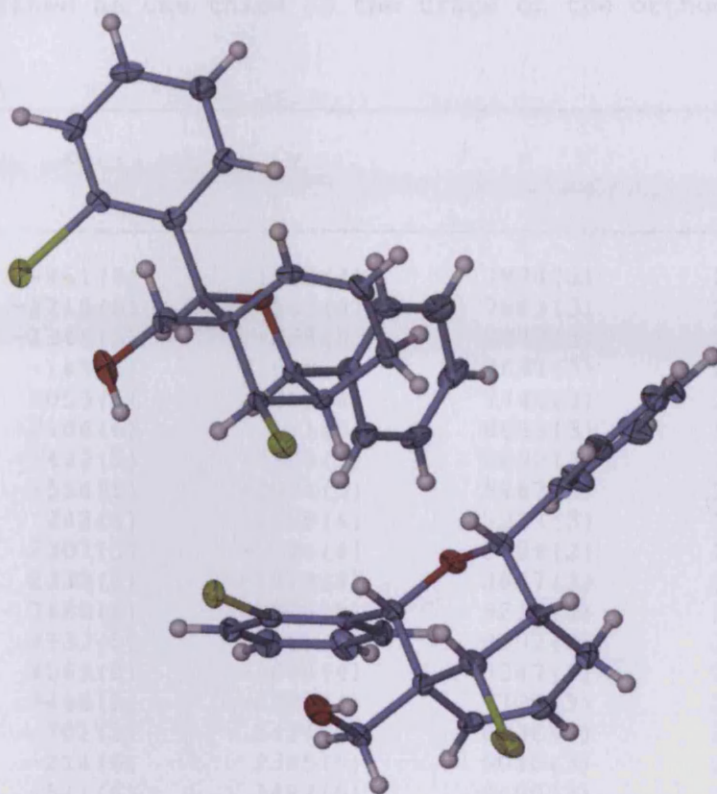
Table 2. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for compound **141**. U(eq) is defined as one third of the trace of the orthogonalised  $U_{ij}$  tensor.

	x	y	z	U(eq)
C(1)	3555(2)	1191(2)	6398(2)	27(1)
C(2)	4703(2)	1393(2)	6866(2)	33(1)
C(3)	5561(2)	509(2)	6889(2)	34(1)
C(4)	5284(2)	-580(2)	6420(2)	32(1)
C(5)	4148(2)	-794(2)	5941(2)	27(1)
C(6)	3280(2)	89(2)	5954(2)	23(1)
C(7)	1986(2)	-2070(2)	6754(2)	22(1)
C(8)	1222(2)	-978(2)	6524(2)	20(1)
C(9)	1043(2)	-97(2)	7425(2)	21(1)
C(10)	-290(2)	202(2)	7409(2)	26(1)
C(11)	-1007(2)	-862(2)	7673(2)	30(1)
C(12)	-428(2)	-1694(2)	8443(2)	31(1)
C(13)	711(2)	-1585(2)	8814(2)	28(1)
C(14)	1541(2)	-625(2)	8494(2)	23(1)
C(15)	2763(2)	-1155(2)	8381(2)	27(1)
C(16)	1681(2)	312(2)	9392(2)	34(1)
C(17)	2646(2)	1198(2)	9309(2)	42(1)
C(18)	3654(3)	1222(3)	9949(2)	59(1)
O(1)	1139(1)	934(1)	5288(1)	27(1)
O(2)	1985(1)	-2879(1)	6137(1)	31(1)
O(3)	2691(1)	-2151(1)	7658(1)	26(1)
O(4)	-2035(1)	-1025(2)	7281(2)	51(1)
S(1)	1795(1)	-218(1)	5372(1)	22(1)

Table 3. Bond lengths [Å] and angles [°] for compound **141**.

C(1)-C(2)	1.385(3)	C(1)-C(6)-S(1)	120.19(16)
C(1)-C(6)	1.386(3)	C(5)-C(6)-S(1)	118.74(16)
C(1)-H(1)	0.9500	O(2)-C(7)-O(3)	118.36(18)
C(2)-C(3)	1.384(3)	O(2)-C(7)-C(8)	121.61(17)
C(2)-H(2)	0.9500	O(3)-C(7)-C(8)	120.03(17)
C(3)-C(4)	1.387(3)	C(7)-C(8)-C(9)	119.33(16)
C(3)-H(3)	0.9500	C(7)-C(8)-S(1)	107.08(13)
C(4)-C(5)	1.381(3)	C(9)-C(8)-S(1)	111.82(13)
C(4)-H(4)	0.9500	C(7)-C(8)-H(8)	105.9
C(5)-C(6)	1.394(3)	C(9)-C(8)-H(8)	105.9
C(5)-H(5)	0.9500	S(1)-C(8)-H(8)	105.9
C(6)-S(1)	1.792(2)	C(10)-C(9)-C(14)	111.39(16)
C(7)-O(2)	1.206(2)	C(10)-C(9)-C(8)	109.28(16)
C(7)-O(3)	1.337(2)	C(14)-C(9)-C(8)	110.40(16)
C(7)-C(8)	1.512(3)	C(10)-C(9)-H(9)	108.6
C(8)-C(9)	1.548(3)	C(14)-C(9)-H(9)	108.6
C(8)-S(1)	1.8707(19)	C(8)-C(9)-H(9)	108.6
C(8)-H(8)	1.0000	C(11)-C(10)-C(9)	111.44(17)
C(9)-C(10)	1.533(3)	C(11)-C(10)-H(10A)	109.3
C(9)-C(14)	1.543(3)	C(9)-C(10)-H(10A)	109.3
C(9)-H(9)	1.0000	C(11)-C(10)-H(10B)	109.3
C(10)-C(11)	1.501(3)	C(9)-C(10)-H(10B)	109.3
C(10)-H(10A)	0.9900	H(10A)-C(10)-H(10B)	108.0
C(10)-H(10B)	0.9900	O(4)-C(11)-C(12)	121.2(2)
C(11)-O(4)	1.226(3)	O(4)-C(11)-C(10)	122.1(2)
C(11)-C(12)	1.464(3)	C(12)-C(11)-C(10)	116.76(18)
C(12)-C(13)	1.325(3)	C(13)-C(12)-C(11)	122.0(2)
C(12)-H(12)	0.9500	C(13)-C(12)-H(12)	119.0
C(13)-C(14)	1.510(3)	C(11)-C(12)-H(12)	119.0
C(13)-H(13)	0.9500	C(12)-C(13)-C(14)	124.70(19)
C(14)-C(15)	1.516(3)	C(12)-C(13)-H(13)	117.6
C(14)-C(16)	1.556(3)	C(14)-C(13)-H(13)	117.6
C(15)-O(3)	1.451(2)	C(13)-C(14)-C(15)	109.44(17)
C(15)-H(15A)	0.9900	C(13)-C(14)-C(9)	109.64(16)
C(15)-H(15B)	0.9900	C(15)-C(14)-C(9)	108.64(16)
C(16)-C(17)	1.485(3)	C(13)-C(14)-C(16)	107.85(17)
C(16)-H(16A)	0.9900	C(15)-C(14)-C(16)	108.13(16)
C(16)-H(16B)	0.9900	C(9)-C(14)-C(16)	113.09(17)
C(17)-C(18)	1.329(4)	O(3)-C(15)-C(14)	111.82(16)
C(17)-H(17A)	0.9500	O(3)-C(15)-H(15A)	109.3
C(18)-H(18A)	0.9500	C(14)-C(15)-H(15A)	109.3
C(18)-H(18B)	0.9500	O(3)-C(15)-H(15B)	109.3
O(1)-S(1)	1.4898(14)	C(14)-C(15)-H(15B)	109.3
		H(15A)-C(15)-H(15B)	107.9
C(2)-C(1)-C(6)	119.0(2)	C(17)-C(16)-C(14)	115.14(19)
C(2)-C(1)-H(1)	120.5	C(17)-C(16)-H(16A)	108.5
C(6)-C(1)-H(1)	120.5	C(14)-C(16)-H(16A)	108.5
C(3)-C(2)-C(1)	120.5(2)	C(17)-C(16)-H(16B)	108.5
C(3)-C(2)-H(2)	119.8	C(14)-C(16)-H(16B)	108.5
C(1)-C(2)-H(2)	119.8	H(16A)-C(16)-H(16B)	107.5
C(2)-C(3)-C(4)	120.1(2)	C(18)-C(17)-C(16)	123.6(3)
C(2)-C(3)-H(3)	120.0	C(18)-C(17)-H(17A)	118.2
C(4)-C(3)-H(3)	120.0	C(16)-C(17)-H(17A)	118.2
C(5)-C(4)-C(3)	120.2(2)	C(17)-C(18)-H(18A)	120.0
C(5)-C(4)-H(4)	119.9	C(17)-C(18)-H(18B)	120.0
C(3)-C(4)-H(4)	119.9	H(18A)-C(18)-H(18B)	120.0
C(4)-C(5)-C(6)	119.1(2)	C(7)-O(3)-C(15)	119.14(15)
C(4)-C(5)-H(5)	120.4	O(1)-S(1)-C(6)	107.16(9)
C(6)-C(5)-H(5)	120.4	O(1)-S(1)-C(8)	104.44(8)
C(1)-C(6)-C(5)	121.06(19)	C(6)-S(1)-C(8)	98.05(9)

Table 1. Crystal data and structure refinement for compound **306**.



Empirical formula	C <sub>21</sub> H <sub>20</sub> BrClO <sub>2</sub>
Formula weight	419.73
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P -1
Unit cell dimensions	a = 10.0220(3) Å, α = 85.5900(10)° b = 10.2660(3) Å, β = 87.1770(10)° c = 18.2060(6) Å, γ = 78.5120(10)°
Volume	1829.08(10) Å <sup>3</sup>
Z, Calculated density	4, 1.524 Mg/m <sup>3</sup>
Absorption coefficient	2.405 mm <sup>-1</sup>
F(000)	856
Crystal size	0.25 x 0.20 x 0.05 mm
Theta range for data collection	3.57 to 25.35°
Limiting indices	-12 ≤ h ≤ 12, -12 ≤ k ≤ 12, -21 ≤ l ≤ 21
Reflections collected / unique	26102 / 6678 [R(int) = 0.1360]
Completeness to theta = 25.35	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8892 and 0.5847
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	6678 / 0 / 451
Goodness-of-fit on F <sup>2</sup>	1.022
Final R indices [I > 2σ(I)]	R <sub>1</sub> = 0.0565, wR <sub>2</sub> = 0.1047
R indices (all data)	R <sub>1</sub> = 0.1068, wR <sub>2</sub> = 0.1206
Largest diff. peak and hole	0.500 and -0.587 e.Å <sup>-3</sup>



Table 2. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for compound **306**.  $U(\text{eq})$  is defined as one third of the trace of the orthogonalised  $U_{ij}$  tensor.

	x	y	z	$U(\text{eq})$
C(11)	-461(5)	1223(4)	7878(3)	21(1)
C(12)	-1718(5)	563(4)	7883(3)	23(1)
C(13)	-1346(5)	-568(5)	7377(3)	27(1)
C(14)	-145(5)	-1600(4)	7698(3)	21(1)
C(15)	1053(5)	-858(4)	7740(3)	23(1)
C(16)	-2166(6)	71(5)	8653(3)	32(1)
C(17)	-1422(5)	-1308(5)	8892(3)	28(1)
C(18)	-554(5)	-2074(5)	8467(3)	26(1)
C(19)	242(5)	-2788(4)	7217(3)	27(1)
C(110)	2307(5)	-1704(4)	8089(2)	20(1)
C(111)	2332(5)	-1919(4)	8857(3)	24(1)
C(112)	3420(6)	-2708(5)	9213(3)	32(1)
C(113)	4533(5)	-3301(5)	8802(3)	30(1)
C(114)	4569(5)	-3096(4)	8047(3)	26(1)
C(115)	3466(5)	-2298(4)	7708(3)	22(1)
C(116)	-701(5)	2434(4)	8336(3)	22(1)
C(117)	-214(6)	2385(5)	9030(3)	33(1)
C(118)	-541(6)	3487(5)	9450(3)	37(2)
C(119)	-1332(5)	4662(5)	9166(3)	34(1)
C(120)	-1795(5)	4718(5)	8456(3)	32(1)
C(121)	-1485(5)	3607(5)	8052(3)	29(1)
O(11)	681(3)	288(3)	8160(2)	22(1)
O(12)	386(4)	-2428(3)	6449(2)	34(1)
Br(11)	3640(1)	-1981(1)	6655(1)	29(1)
Cl(11)	-2798(1)	-1301(1)	7240(1)	43(1)
C(21)	4495(5)	1770(4)	7399(2)	20(1)
C(22)	3186(5)	1944(4)	6959(3)	22(1)
C(23)	3645(5)	1639(4)	6183(2)	19(1)
C(24)	4477(5)	2657(4)	5848(2)	18(1)
C(25)	5757(5)	2464(4)	6338(2)	19(1)
C(26)	2257(5)	3319(4)	6976(3)	28(1)
C(27)	2621(5)	4312(5)	6399(3)	29(1)
C(28)	3610(5)	4022(4)	5891(3)	22(1)
C(29)	4913(5)	2414(4)	5046(2)	25(1)
C(210)	6717(5)	3420(4)	6150(2)	20(1)
C(211)	6375(5)	4711(4)	6385(2)	23(1)
C(212)	7251(5)	5592(5)	6283(3)	26(1)
C(213)	8521(6)	5210(5)	5935(3)	31(1)
C(214)	8887(5)	3952(5)	5684(3)	27(1)
C(215)	7984(5)	3063(4)	5791(2)	20(1)
C(216)	4253(5)	1969(5)	8208(3)	25(1)
C(217)	3964(5)	926(5)	8664(3)	28(1)
C(218)	3750(5)	1048(5)	9422(3)	30(1)
C(219)	3813(6)	2215(5)	9715(3)	37(1)
C(220)	4097(6)	3277(6)	9261(3)	46(2)
C(221)	4325(6)	3139(5)	8508(3)	36(1)
O(21)	5337(3)	2675(3)	7094(2)	21(1)
O(22)	5644(4)	1126(3)	4930(2)	36(1)
Br(21)	8619(1)	1333(1)	5443(1)	31(1)
Cl(21)	2212(1)	1552(1)	5638(1)	30(1)

Table 3. Bond lengths [Å] and angles [°] for compound **306**.

C(11)-O(11)	1.428(5)	C(25)-O(21)	1.439(5)
C(11)-C(116)	1.524(6)	C(25)-C(210)	1.516(6)
C(11)-C(12)	1.544(6)	C(25)-H(25)	1.0000
C(11)-H(11)	1.0000	C(26)-C(27)	1.490(6)
C(12)-C(13)	1.515(6)	C(26)-H(26A)	0.9900
C(12)-C(16)	1.530(6)	C(26)-H(26B)	0.9900
C(12)-H(12)	1.0000	C(27)-C(28)	1.327(6)
C(13)-C(14)	1.542(6)	C(27)-H(27)	0.9500
C(13)-Cl(11)	1.801(5)	C(28)-H(28)	0.9500
C(13)-H(13)	1.0000	C(29)-O(22)	1.405(5)
C(14)-C(18)	1.511(6)	C(29)-H(29A)	0.9900
C(14)-C(19)	1.533(6)	C(29)-H(29B)	0.9900
C(14)-C(15)	1.552(6)	C(210)-C(215)	1.394(6)
C(15)-O(11)	1.430(5)	C(210)-C(211)	1.396(6)
C(15)-C(110)	1.516(6)	C(211)-C(212)	1.377(7)
C(15)-H(15)	1.0000	C(211)-H(211)	0.9500
C(16)-C(17)	1.505(6)	C(212)-C(213)	1.391(7)
C(16)-H(16A)	0.9900	C(212)-H(212)	0.9500
C(16)-H(16B)	0.9900	C(213)-C(214)	1.377(6)
C(17)-C(18)	1.314(6)	C(213)-H(213)	0.9500
C(17)-H(17)	0.9500	C(214)-C(215)	1.405(7)
C(18)-H(18)	0.9500	C(214)-H(214)	0.9500
C(19)-O(12)	1.425(5)	C(215)-Br(21)	1.909(4)
C(19)-H(19A)	0.9900	C(216)-C(217)	1.372(6)
C(19)-H(19B)	0.9900	C(216)-C(221)	1.374(6)
C(110)-C(115)	1.381(6)	C(217)-C(218)	1.398(6)
C(110)-C(111)	1.399(6)	C(217)-H(217)	0.9500
C(111)-C(112)	1.379(6)	C(218)-C(219)	1.361(7)
C(111)-H(111)	0.9500	C(218)-H(218)	0.9500
C(112)-C(113)	1.376(7)	C(219)-C(220)	1.383(7)
C(112)-H(112)	0.9500	C(219)-H(219)	0.9500
C(113)-C(114)	1.374(7)	C(220)-C(221)	1.393(7)
C(113)-H(113)	0.9500	C(220)-H(220)	0.9500
C(114)-C(115)	1.380(6)	C(221)-H(221)	0.9500
C(114)-H(114)	0.9500	O(22)-H(22A)	0.8400
C(115)-Br(11)	1.924(5)		
C(116)-C(117)	1.370(6)	O(11)-C(11)-C(116)	108.3(4)
C(116)-C(121)	1.379(6)	O(11)-C(11)-C(12)	110.2(3)
C(117)-C(118)	1.390(7)	C(116)-C(11)-C(12)	112.6(4)
C(117)-H(117)	0.9500	O(11)-C(11)-H(11)	108.6
C(118)-C(119)	1.383(7)	C(116)-C(11)-H(11)	108.6
C(118)-H(118)	0.9500	C(12)-C(11)-H(11)	108.6
C(119)-C(120)	1.388(7)	C(13)-C(12)-C(16)	111.5(4)
C(119)-H(119)	0.9500	C(13)-C(12)-C(11)	106.3(4)
C(120)-C(121)	1.379(7)	C(16)-C(12)-C(11)	113.7(4)
C(120)-H(120)	0.9500	C(13)-C(12)-H(12)	108.4
C(121)-H(121)	0.9500	C(16)-C(12)-H(12)	108.4
O(12)-H(12A)	0.8400	C(11)-C(12)-H(12)	108.4
C(21)-O(21)	1.438(5)	C(12)-C(13)-C(14)	109.0(4)
C(21)-C(216)	1.504(6)	C(12)-C(13)-Cl(11)	111.0(3)
C(21)-C(22)	1.544(7)	C(14)-C(13)-Cl(11)	112.1(3)
C(21)-H(21)	1.0000	C(12)-C(13)-H(13)	108.2
C(22)-C(23)	1.500(6)	C(14)-C(13)-H(13)	108.2
C(22)-C(26)	1.530(6)	Cl(11)-C(13)-H(13)	108.2
C(22)-H(22)	1.0000	C(18)-C(14)-C(19)	109.8(4)
C(23)-C(24)	1.536(6)	C(18)-C(14)-C(13)	108.7(4)
C(23)-Cl(21)	1.806(5)	C(19)-C(14)-C(13)	111.0(4)
C(23)-H(23)	1.0000	C(18)-C(14)-C(15)	109.3(4)
C(24)-C(28)	1.500(6)	C(19)-C(14)-C(15)	111.4(4)
C(24)-C(29)	1.527(6)	C(13)-C(14)-C(15)	106.5(4)
C(24)-C(25)	1.570(6)	O(11)-C(15)-C(110)	106.1(4)



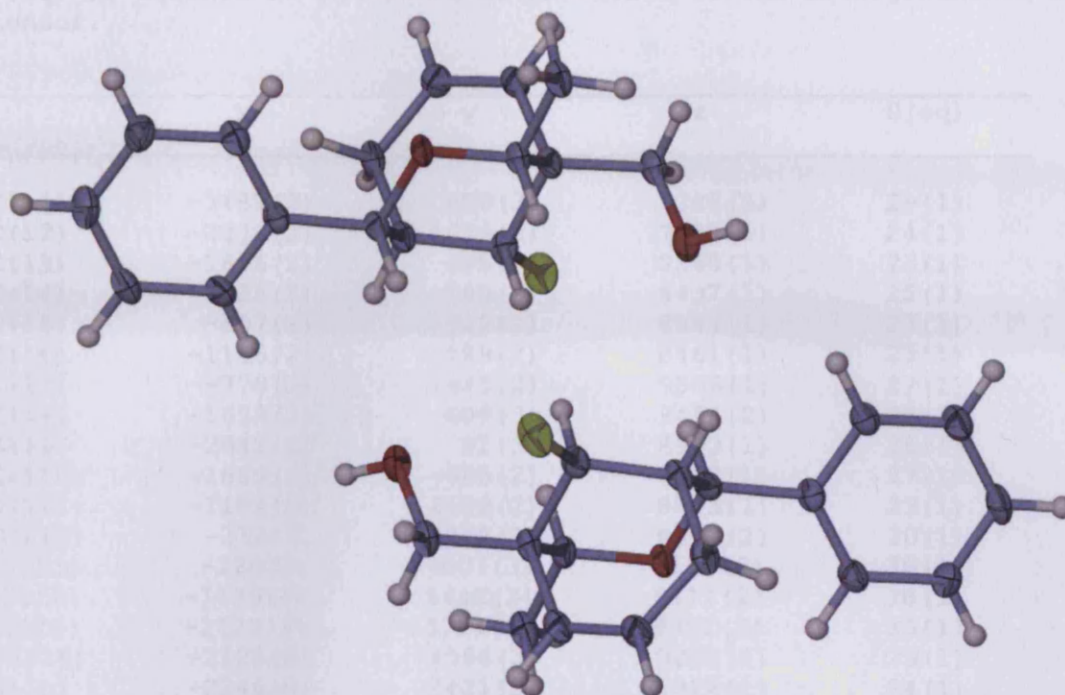
O(11)-C(15)-C(14) 111.9(4)  
C(110)-C(15)-C(14) 113.9(4)  
O(11)-C(15)-H(15) 108.2  
C(110)-C(15)-H(15) 108.2  
C(14)-C(15)-H(15) 108.2  
C(17)-C(16)-C(12) 113.4(4)  
C(17)-C(16)-H(16A) 108.9  
C(12)-C(16)-H(16A) 108.9  
C(17)-C(16)-H(16B) 108.9  
C(12)-C(16)-H(16B) 108.9  
H(16A)-C(16)-H(16B) 107.7  
C(18)-C(17)-C(16) 124.2(5)  
C(18)-C(17)-H(17) 117.9  
C(16)-C(17)-H(17) 117.9  
C(17)-C(18)-C(14) 122.1(4)  
C(17)-C(18)-H(18) 118.9  
C(14)-C(18)-H(18) 118.9  
O(12)-C(19)-C(14) 114.3(4)  
O(12)-C(19)-H(19A) 108.7  
C(14)-C(19)-H(19A) 108.7  
O(12)-C(19)-H(19B) 108.7  
C(14)-C(19)-H(19B) 108.7  
H(19A)-C(19)-H(19B) 107.6  
C(115)-C(110)-C(111) 115.7(4)  
C(115)-C(110)-C(15) 125.1(4)  
C(111)-C(110)-C(15) 119.2(4)  
C(112)-C(111)-C(110) 122.5(5)  
C(112)-C(111)-H(111) 118.7  
C(110)-C(111)-H(111) 118.7  
C(113)-C(112)-C(111) 119.1(5)  
C(113)-C(112)-H(112) 120.4  
C(111)-C(112)-H(112) 120.4  
C(114)-C(113)-C(112) 120.5(5)  
C(114)-C(113)-H(113) 119.8  
C(112)-C(113)-H(113) 119.8  
C(113)-C(114)-C(115) 119.0(5)  
C(113)-C(114)-H(114) 120.5  
C(115)-C(114)-H(114) 120.5  
C(114)-C(115)-C(110) 123.2(4)  
C(114)-C(115)-Br(11) 116.3(4)  
C(110)-C(115)-Br(11) 120.4(4)  
C(117)-C(116)-C(121) 119.0(4)  
C(117)-C(116)-C(11) 122.4(4)  
C(121)-C(116)-C(11) 118.5(4)  
C(116)-C(117)-C(118) 120.5(5)  
C(116)-C(117)-H(117) 119.7  
C(118)-C(117)-H(117) 119.7  
C(119)-C(118)-C(117) 120.5(5)  
C(119)-C(118)-H(118) 119.8  
C(117)-C(118)-H(118) 119.8  
C(118)-C(119)-C(120) 118.8(5)  
C(118)-C(119)-H(119) 120.6  
C(120)-C(119)-H(119) 120.6  
C(121)-C(120)-C(119) 120.0(5)  
C(121)-C(120)-H(120) 120.0  
C(119)-C(120)-H(120) 120.0  
C(116)-C(121)-C(120) 121.2(5)  
C(116)-C(121)-H(121) 119.4  
C(120)-C(121)-H(121) 119.4  
C(11)-O(11)-C(15) 113.1(3)  
C(19)-O(12)-H(12A) 109.5  
O(21)-C(21)-C(216) 108.3(4)  
O(21)-C(21)-C(22) 110.3(3)  
C(216)-C(21)-C(22) 114.6(4)

O(21)-C(21)-H(21) 107.8  
C(216)-C(21)-H(21) 107.8  
C(22)-C(21)-H(21) 107.8  
C(23)-C(22)-C(26) 110.8(4)  
C(23)-C(22)-C(21) 106.1(4)  
C(26)-C(22)-C(21) 114.9(4)  
C(23)-C(22)-H(22) 108.3  
C(26)-C(22)-H(22) 108.3  
C(21)-C(22)-H(22) 108.3  
C(22)-C(23)-C(24) 110.1(4)  
C(22)-C(23)-Cl(21) 110.8(3)  
C(24)-C(23)-Cl(21) 112.7(3)  
C(22)-C(23)-H(23) 107.7  
C(24)-C(23)-H(23) 107.7  
Cl(21)-C(23)-H(23) 107.7  
C(28)-C(24)-C(29) 109.7(4)  
C(28)-C(24)-C(23) 108.1(4)  
C(29)-C(24)-C(23) 111.7(4)  
C(28)-C(24)-C(25) 111.7(4)  
C(29)-C(24)-C(25) 110.5(4)  
C(23)-C(24)-C(25) 105.2(3)  
O(21)-C(25)-C(210) 104.1(4)  
O(21)-C(25)-C(24) 110.2(4)  
C(210)-C(25)-C(24) 115.9(3)  
O(21)-C(25)-H(25) 108.8  
C(210)-C(25)-H(25) 108.8  
C(24)-C(25)-H(25) 108.8  
C(27)-C(26)-C(22) 113.7(4)  
C(27)-C(26)-H(26A) 108.8  
C(22)-C(26)-H(26A) 108.8  
C(27)-C(26)-H(26B) 108.8  
C(22)-C(26)-H(26B) 108.8  
H(26A)-C(26)-H(26B) 107.7  
C(28)-C(27)-C(26) 123.6(4)  
C(28)-C(27)-H(27) 118.2  
C(26)-C(27)-H(27) 118.2  
C(27)-C(28)-C(24) 122.8(4)  
C(27)-C(28)-H(28) 118.6  
C(24)-C(28)-H(28) 118.6  
O(22)-C(29)-C(24) 114.9(3)  
O(22)-C(29)-H(29A) 108.5  
C(24)-C(29)-H(29A) 108.5  
O(22)-C(29)-H(29B) 108.5  
C(24)-C(29)-H(29B) 108.5  
H(29A)-C(29)-H(29B) 107.5  
C(215)-C(210)-C(211) 116.9(4)  
C(215)-C(210)-C(25) 123.6(4)  
C(211)-C(210)-C(25) 119.3(4)  
C(212)-C(211)-C(210) 122.1(5)  
C(212)-C(211)-H(211) 119.0  
C(210)-C(211)-H(211) 119.0  
C(211)-C(212)-C(213) 120.2(5)  
C(211)-C(212)-H(212) 119.9  
C(213)-C(212)-H(212) 119.9  
C(214)-C(213)-C(212) 119.5(5)  
C(214)-C(213)-H(213) 120.3  
C(212)-C(213)-H(213) 120.3  
C(213)-C(214)-C(215) 119.8(5)  
C(213)-C(214)-H(214) 120.1  
C(215)-C(214)-H(214) 120.1  
C(210)-C(215)-C(214) 121.6(4)  
C(210)-C(215)-Br(21) 122.4(3)  
C(214)-C(215)-Br(21) 116.1(4)  
C(217)-C(216)-C(221) 118.9(5)

C(217)-C(216)-C(21)	118.2(4)	C(220)-C(219)-H(219)	120.0
C(221)-C(216)-C(21)	122.8(4)	C(219)-C(220)-C(221)	119.6(5)
C(216)-C(217)-C(218)	120.7(5)	C(219)-C(220)-H(220)	120.2
C(216)-C(217)-H(217)	119.7	C(221)-C(220)-H(220)	120.2
C(218)-C(217)-H(217)	119.7	C(216)-C(221)-C(220)	120.8(5)
C(219)-C(218)-C(217)	120.1(4)	C(216)-C(221)-H(221)	119.6
C(219)-C(218)-H(218)	120.0	C(220)-C(221)-H(221)	119.6
C(217)-C(218)-H(218)	120.0	C(21)-O(21)-C(25)	112.8(3)
C(218)-C(219)-C(220)	119.9(5)	C(29)-O(22)-H(22A)	109.5
C(218)-C(219)-H(219)	120.0		

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Table 1. Crystal data and structure refinement for compound **321**.



Empirical formula	C <sub>16</sub> H <sub>19</sub> ClO <sub>2</sub>
Formula weight	278.76
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P 2 <sub>1</sub> /n
Unit cell dimensions	a = 12.1680(5) Å, α = 90° b = 10.6880(4) Å, β = 95.458(2)° c = 21.0670(9) Å, γ = 90°
Volume	2727.38(19) Å <sup>3</sup>
Z, Calculated density	8, 1.358 Mg/m <sup>3</sup>
Absorption coefficient	0.275 mm <sup>-1</sup>
F(000)	1184
Crystal size	0.25 x 0.20 x 0.13 mm
Theta range for data collection	3.75 to 26.37°
Limiting indices	-14 ≤ h ≤ 15, -9 ≤ k ≤ 13, -25 ≤ l ≤ 26
Reflections collected / unique	12492 / 5333 [R(int) = 0.0685]
Completeness to theta = 26.37	95.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9651 and 0.9343
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	5333 / 0 / 347
Goodness-of-fit on F <sup>2</sup>	1.108
Final R indices [I > 2σ(I)]	R <sub>1</sub> = 0.0703, wR <sub>2</sub> = 0.1484
R indices (all data)	R <sub>1</sub> = 0.1033, wR <sub>2</sub> = 0.1632
Largest diff. peak and hole	0.306 and -0.313 e.Å <sup>-3</sup>

Table 2. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for compound **321**. U(eq) is defined as one third of the trace of the orthogonalised  $U_{ij}$  tensor.

	x	y	z	U(eq)
C(11)	-3487(2)	950(3)	7785(2)	29(1)
C(12)	-2278(2)	1279(2)	7957(1)	24(1)
C(13)	-1606(2)	235(2)	8340(1)	23(1)
C(14)	-425(2)	745(2)	8437(1)	25(1)
C(15)	-407(2)	1922(2)	8844(1)	23(1)
C(16)	-1146(2)	2889(2)	8461(1)	23(1)
C(17)	-770(2)	1645(2)	9506(1)	27(1)
C(18)	-1679(3)	689(3)	9494(2)	28(1)
C(19)	-2042(2)	41(3)	8983(1)	26(1)
C(110)	-1669(3)	-985(2)	7967(1)	27(1)
C(111)	-1182(2)	4132(2)	8803(1)	23(1)
C(112)	-232(3)	4868(3)	8870(2)	30(1)
C(113)	-230(3)	6007(3)	9177(2)	<b>36(1)</b>
C(114)	-1179(3)	6448(3)	9411(2)	<b>38(1)</b>
C(115)	-2125(3)	5724(3)	9351(2)	<b>33(1)</b>
C(116)	-2126(2)	4566(3)	9055(2)	29(1)
O(11)	-2246(2)	2421(2)	8322(1)	24(1)
O(12)	-1276(2)	-800(2)	7358(1)	34(1)
Cl(11)	541(1)	-391(1)	8801(1)	35(1)
C(21)	3509(2)	1568(3)	7207(2)	32(1)
C(22)	2305(2)	1245(2)	7038(1)	24(1)
C(23)	1625(2)	2311(2)	6681(1)	24(1)
C(24)	446(2)	1800(2)	6570(2)	27(1)
C(25)	438(2)	662(2)	6140(1)	24(1)
C(26)	1163(2)	-330(2)	6510(1)	23(1)
C(27)	825(2)	1004(3)	5490(1)	28(1)
C(28)	1705(3)	1982(3)	5517(2)	30(1)
C(29)	2057(2)	2582(3)	6049(1)	28(1)
C(210)	1689(3)	3500(3)	7082(2)	30(1)
C(211)	1191(2)	-1564(2)	6160(1)	24(1)
C(212)	2090(2)	-1954(3)	5856(2)	<b>29(1)</b>
C(213)	2071(3)	-3103(3)	5547(2)	<b>33(1)</b>
C(214)	1153(3)	-3867(3)	5532(2)	<b>34(1)</b>
C(215)	243(3)	-3481(3)	5829(2)	33(1)
C(216)	266(3)	-2342(3)	6142(2)	29(1)
O(21)	2267(2)	122(2)	6652(1)	24(1)
O(22)	1312(2)	3258(2)	7691(1)	34(1)
Cl(21)	-520(1)	2963(1)	6227(1)	40(1)

Table 3. Bond lengths [Å] and angles [°] for compound **321**.

C(11)-C(12)	1.522(4)	C(27)-H(27B)	0.9900
C(11)-H(11A)	0.9800	C(28)-C(29)	1.326(4)
C(11)-H(11B)	0.9800	C(28)-H(28)	0.9500
C(11)-H(11C)	0.9800	C(29)-H(29)	0.9500
C(12)-O(11)	1.441(3)	C(210)-O(22)	1.428(4)
C(12)-C(13)	1.563(4)	C(210)-H(21D)	0.9900
C(12)-H(12)	1.0000	C(210)-H(21E)	0.9900
C(13)-C(19)	1.514(4)	C(211)-C(212)	1.384(4)
C(13)-C(110)	1.520(4)	C(211)-C(216)	1.397(4)
C(13)-C(14)	1.533(4)	C(212)-C(213)	1.388(4)
C(14)-C(15)	1.521(4)	C(212)-H(212)	0.9500
C(14)-Cl(11)	1.809(3)	C(213)-C(214)	1.382(4)
C(14)-H(14)	1.0000	C(213)-H(213)	0.9500
C(15)-C(17)	1.531(4)	C(214)-C(215)	1.384(4)
C(15)-C(16)	1.546(4)	C(214)-H(214)	0.9500
C(15)-H(15)	1.0000	C(215)-C(216)	1.384(4)
C(16)-O(11)	1.433(3)	C(215)-H(215)	0.9500
C(16)-C(111)	1.513(4)	C(216)-H(216)	0.9500
C(16)-H(16)	1.0000	O(22)-H(22A)	0.8400
C(17)-C(18)	1.505(4)		
C(17)-H(17A)	0.9900	C(12)-C(11)-H(11A)	109.5
C(17)-H(17B)	0.9900	C(12)-C(11)-H(11B)	109.5
C(18)-C(19)	1.320(4)	H(11A)-C(11)-H(11B)	109.5
C(18)-H(18)	0.9500	C(12)-C(11)-H(11C)	109.5
C(19)-H(19)	0.9500	H(11A)-C(11)-H(11C)	109.5
C(110)-O(12)	1.426(4)	H(11B)-C(11)-H(11C)	109.5
C(110)-H(11D)	0.9900	O(11)-C(12)-C(11)	107.4(2)
C(110)-H(11E)	0.9900	O(11)-C(12)-C(13)	110.0(2)
C(111)-C(116)	1.390(4)	C(11)-C(12)-C(13)	113.8(2)
C(111)-C(112)	1.395(4)	O(11)-C(12)-H(12)	108.5
C(112)-C(113)	1.378(4)	C(11)-C(12)-H(12)	108.5
C(112)-H(112)	0.9500	C(13)-C(12)-H(12)	108.5
C(113)-C(114)	1.381(5)	C(19)-C(13)-C(110)	109.9(2)
C(113)-H(113)	0.9500	C(19)-C(13)-C(14)	109.5(2)
C(114)-C(115)	1.383(4)	C(110)-C(13)-C(14)	112.0(2)
C(114)-H(114)	0.9500	C(19)-C(13)-C(12)	110.4(2)
C(115)-C(116)	1.386(4)	C(110)-C(13)-C(12)	110.3(2)
C(115)-H(115)	0.9500	C(14)-C(13)-C(12)	104.6(2)
C(116)-H(116)	0.9500	C(15)-C(14)-C(13)	109.4(2)
O(12)-H(12A)	0.8400	C(15)-C(14)-Cl(11)	110.01(19)
C(21)-C(22)	1.514(4)	C(13)-C(14)-Cl(11)	112.35(19)
C(21)-H(21A)	0.9800	C(15)-C(14)-H(14)	108.3
C(21)-H(21B)	0.9800	C(13)-C(14)-H(14)	108.3
C(21)-H(21C)	0.9800	Cl(11)-C(14)-H(14)	108.3
C(22)-O(21)	1.449(3)	C(14)-C(15)-C(17)	111.3(2)
C(22)-C(23)	1.559(4)	C(14)-C(15)-C(16)	106.4(2)
C(22)-H(22)	1.0000	C(17)-C(15)-C(16)	113.6(2)
C(23)-C(29)	1.506(4)	C(14)-C(15)-H(15)	108.5
C(23)-C(210)	1.524(4)	C(17)-C(15)-H(15)	108.5
C(23)-C(24)	1.532(4)	C(16)-C(15)-H(15)	108.5
C(24)-C(25)	1.515(4)	O(11)-C(16)-C(111)	109.6(2)
C(24)-Cl(21)	1.813(3)	O(11)-C(16)-C(15)	111.1(2)
C(24)-H(24)	1.0000	C(111)-C(16)-C(15)	112.4(2)
C(25)-C(27)	1.535(4)	O(11)-C(16)-H(16)	107.9
C(25)-C(26)	1.543(4)	C(111)-C(16)-H(16)	107.9
C(25)-H(25)	1.0000	C(15)-C(16)-H(16)	107.9
C(26)-O(21)	1.432(3)	C(18)-C(17)-C(15)	113.1(2)
C(26)-C(211)	1.512(4)	C(18)-C(17)-H(17A)	109.0
C(26)-H(26)	1.0000	C(15)-C(17)-H(17A)	109.0
C(27)-C(28)	1.494(4)	C(18)-C(17)-H(17B)	109.0
C(27)-H(27A)	0.9900	C(15)-C(17)-H(17B)	109.0

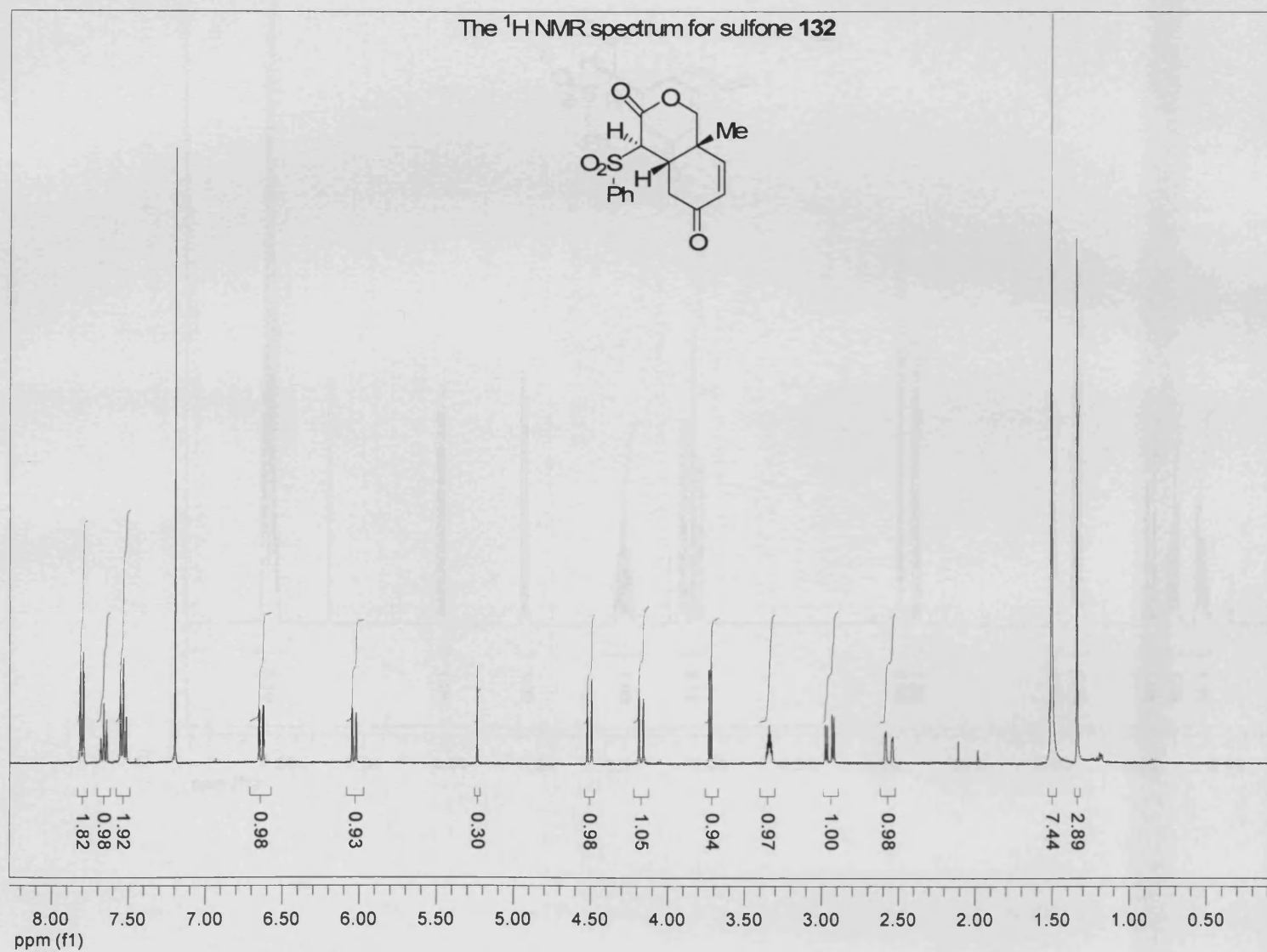
H(17A)-C(17)-H(17B)	107.8
C(19)-C(18)-C(17)	123.9(3)
C(19)-C(18)-H(18)	118.0
C(17)-C(18)-H(18)	118.0
C(18)-C(19)-C(13)	122.6(3)
C(18)-C(19)-H(19)	118.7
C(13)-C(19)-H(19)	118.7
O(12)-C(110)-C(13)	110.0(2)
O(12)-C(110)-H(11D)	109.7
C(13)-C(110)-H(11D)	109.7
O(12)-C(110)-H(11E)	109.7
C(13)-C(110)-H(11E)	109.7
H(11D)-C(110)-H(11E)	108.2
C(116)-C(111)-C(112)	118.7(3)
C(116)-C(111)-C(16)	122.5(3)
C(112)-C(111)-C(16)	118.8(3)
C(113)-C(112)-C(111)	120.7(3)
C(113)-C(112)-H(112)	119.7
C(111)-C(112)-H(112)	119.7
C(112)-C(113)-C(114)	120.3(3)
C(112)-C(113)-H(113)	119.8
C(114)-C(113)-H(113)	119.8
C(113)-C(114)-C(115)	119.6(3)
C(113)-C(114)-H(114)	120.2
C(115)-C(114)-H(114)	120.2
C(114)-C(115)-C(116)	120.4(3)
C(114)-C(115)-H(115)	119.8
C(116)-C(115)-H(115)	119.8
C(115)-C(116)-C(111)	120.3(3)
C(115)-C(116)-H(116)	119.8
C(111)-C(116)-H(116)	119.8
C(16)-O(11)-C(12)	112.5(2)
C(110)-O(12)-H(12A)	109.5
C(22)-C(21)-H(21A)	109.5
C(22)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
C(22)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
O(21)-C(22)-C(21)	107.4(2)
O(21)-C(22)-C(23)	110.3(2)
C(21)-C(22)-C(23)	113.8(2)
O(21)-C(22)-H(22)	108.4
C(21)-C(22)-H(22)	108.4
C(23)-C(22)-H(22)	108.4
C(29)-C(23)-C(210)	109.0(2)
C(29)-C(23)-C(24)	109.5(2)
C(210)-C(23)-C(24)	112.3(2)
C(29)-C(23)-C(22)	110.7(2)
C(210)-C(23)-C(22)	110.2(2)
C(24)-C(23)-C(22)	105.0(2)
C(25)-C(24)-C(23)	109.3(2)
C(25)-C(24)-Cl(21)	110.2(2)
C(23)-C(24)-Cl(21)	112.24(19)

C(25)-C(24)-H(24)	108.3
C(23)-C(24)-H(24)	108.3
Cl(21)-C(24)-H(24)	108.3
C(24)-C(25)-C(27)	111.0(2)
C(24)-C(25)-C(26)	106.2(2)
C(27)-C(25)-C(26)	113.9(2)
C(24)-C(25)-H(25)	108.5
C(27)-C(25)-H(25)	108.5
C(26)-C(25)-H(25)	108.5
O(21)-C(26)-C(211)	109.4(2)
O(21)-C(26)-C(25)	110.7(2)
C(211)-C(26)-C(25)	113.1(2)
O(21)-C(26)-H(26)	107.8
C(211)-C(26)-H(26)	107.8
C(25)-C(26)-H(26)	107.8
C(28)-C(27)-C(25)	114.3(2)
C(28)-C(27)-H(27A)	108.7
C(25)-C(27)-H(27A)	108.7
C(28)-C(27)-H(27B)	108.7
C(25)-C(27)-H(27B)	108.7
H(27A)-C(27)-H(27B)	107.6
C(29)-C(28)-C(27)	122.9(3)
C(29)-C(28)-H(28)	118.5
C(27)-C(28)-H(28)	118.5
C(28)-C(29)-C(23)	122.8(3)
C(28)-C(29)-H(29)	118.6
C(23)-C(29)-H(29)	118.6
O(22)-C(210)-C(23)	110.1(2)
O(22)-C(210)-H(21D)	109.6
C(23)-C(210)-H(21D)	109.6
O(22)-C(210)-H(21E)	109.6
C(23)-C(210)-H(21E)	109.6
H(21D)-C(210)-H(21E)	108.2
C(212)-C(211)-C(216)	118.5(3)
C(212)-C(211)-C(26)	123.0(3)
C(216)-C(211)-C(26)	118.5(3)
C(211)-C(212)-C(213)	120.3(3)
C(211)-C(212)-H(212)	119.8
C(213)-C(212)-H(212)	119.8
C(214)-C(213)-C(212)	120.7(3)
C(214)-C(213)-H(213)	119.6
C(212)-C(213)-H(213)	119.6
C(213)-C(214)-C(215)	119.5(3)
C(213)-C(214)-H(214)	120.3
C(215)-C(214)-H(214)	120.3
C(216)-C(215)-C(214)	119.8(3)
C(216)-C(215)-H(215)	120.1
C(214)-C(215)-H(215)	120.1
C(215)-C(216)-C(211)	121.1(3)
C(215)-C(216)-H(216)	119.4
C(211)-C(216)-H(216)	119.4
C(26)-O(21)-C(22)	112.1(2)
C(210)-O(22)-H(22A)	109.5

## **Appendix C**

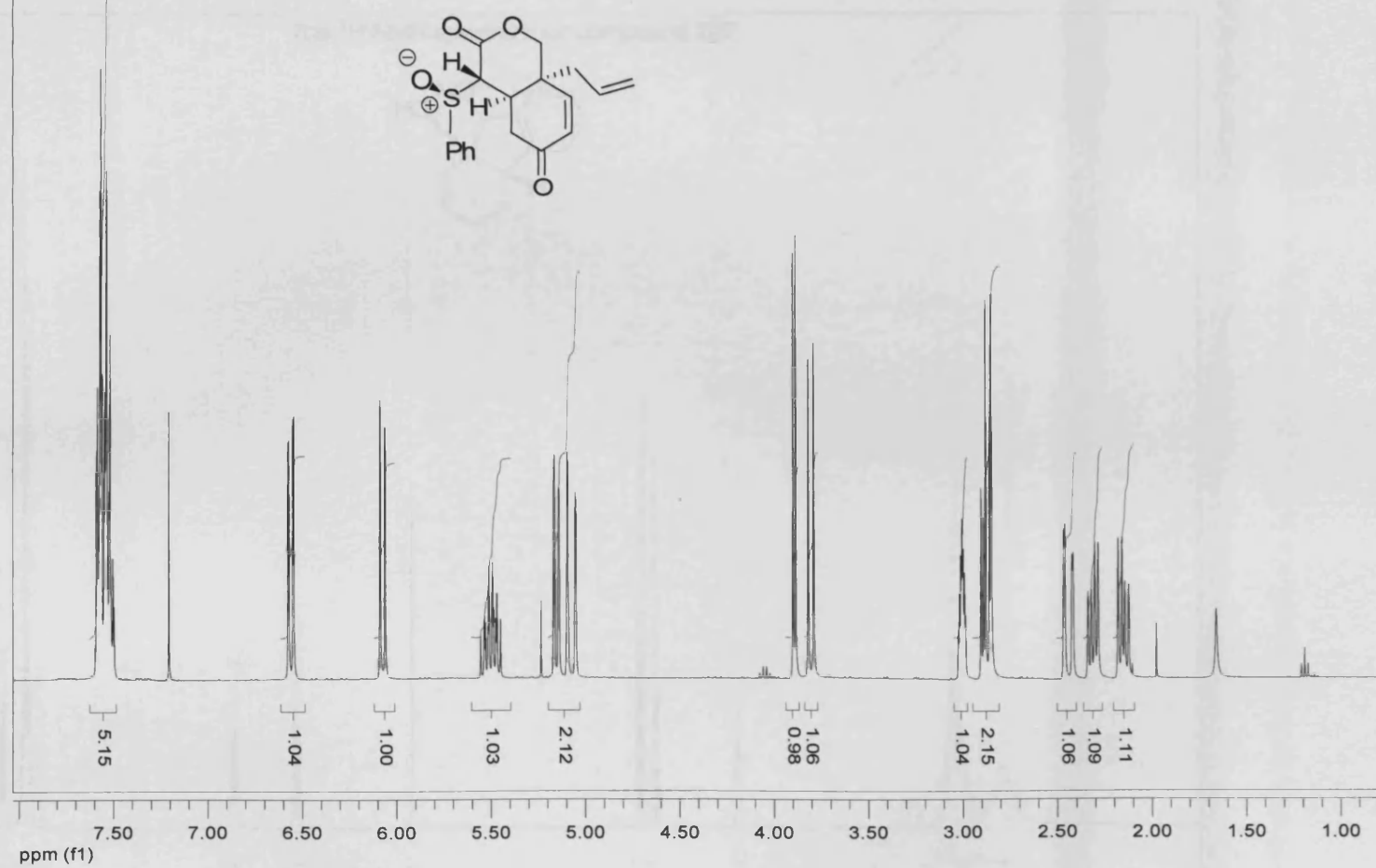
### **$^1\text{H}$ NMR Spectra of Selected Compounds**

The  $^1\text{H}$  NMR spectrum for sulfone **132**

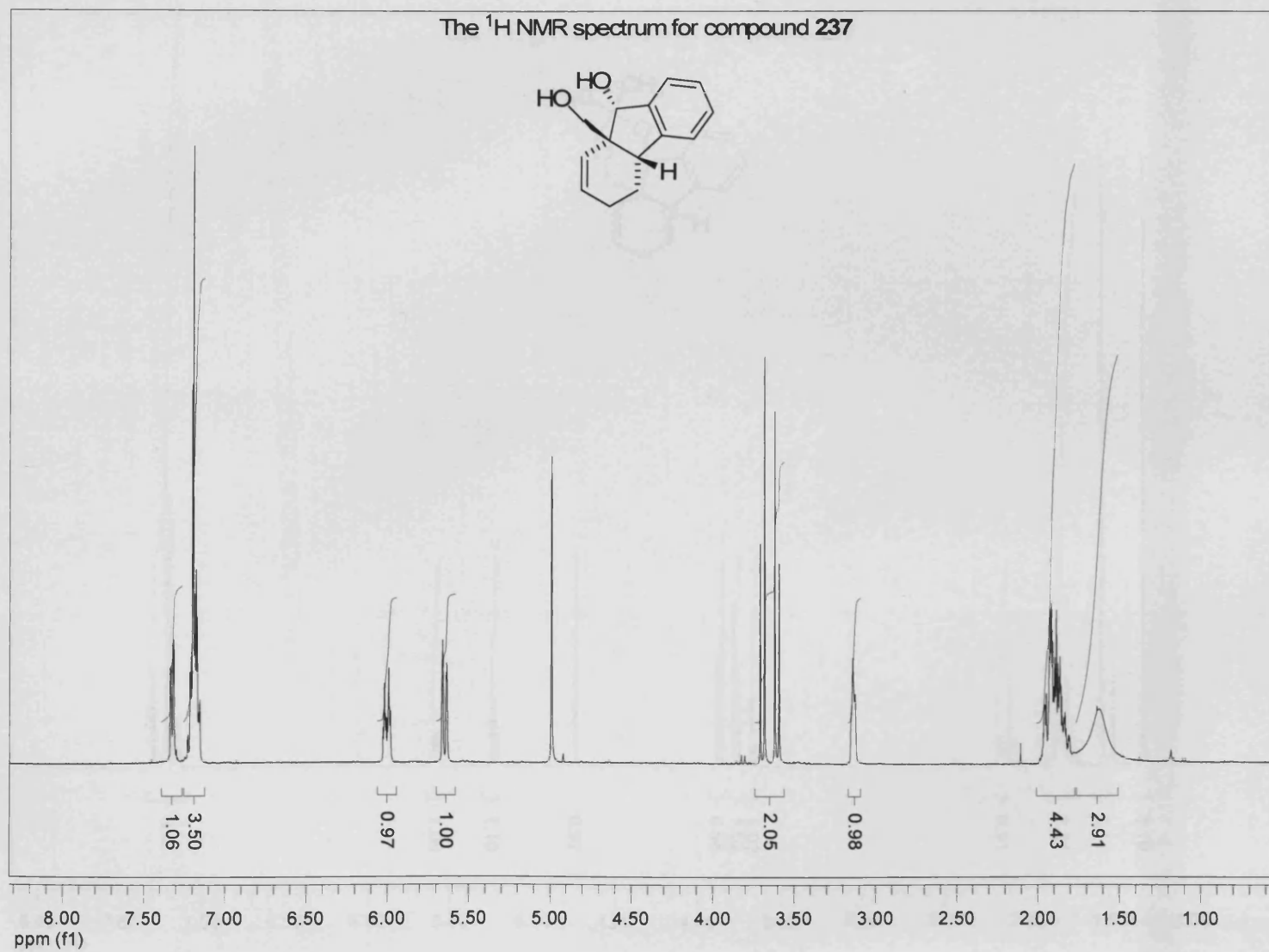
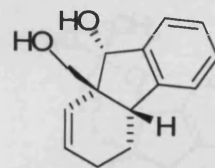




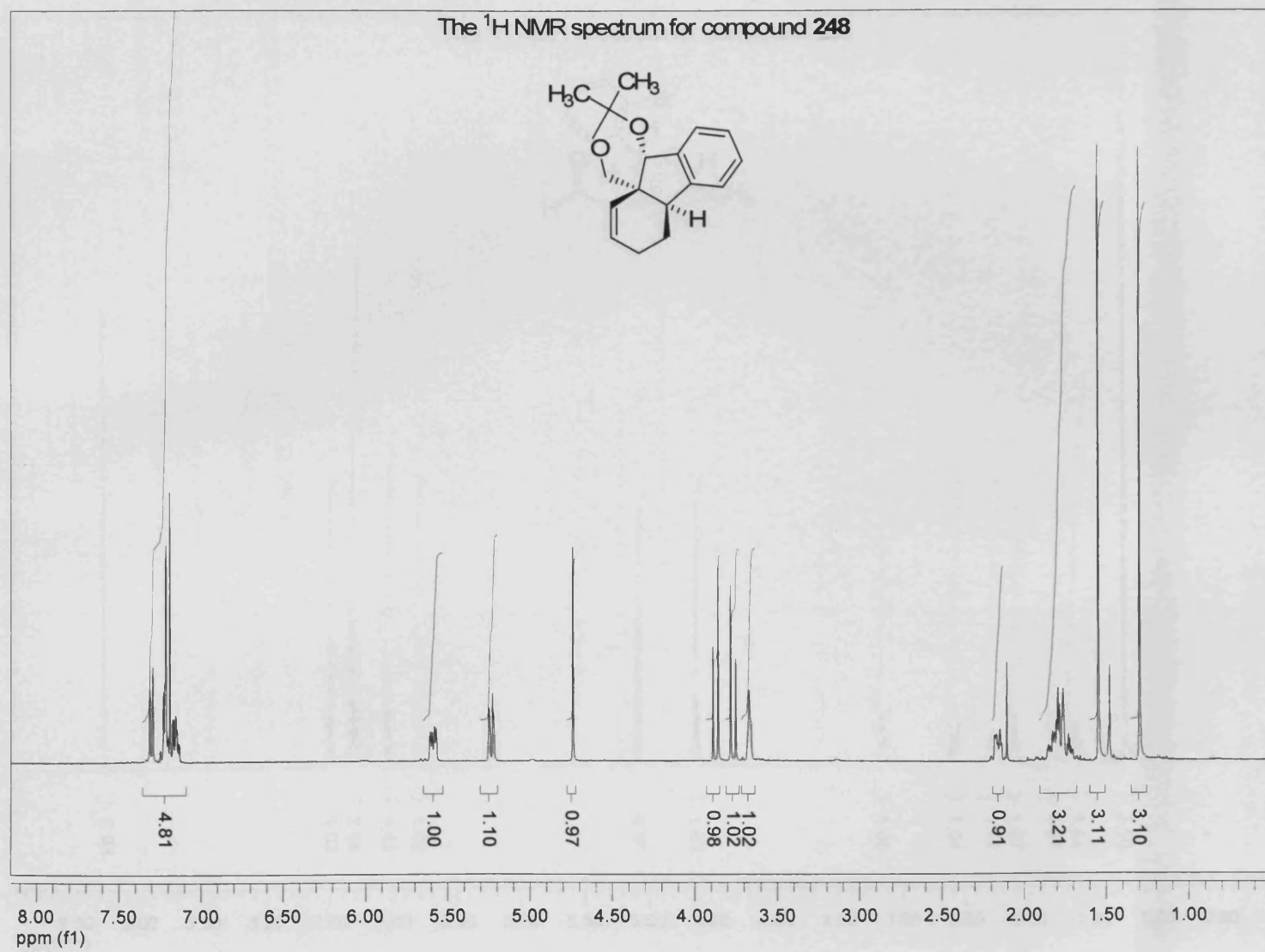
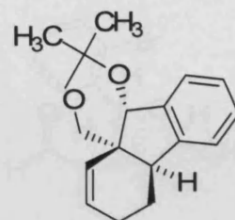
The  $^1\text{H}$  NMR spectrum for major sulfoxide **141**



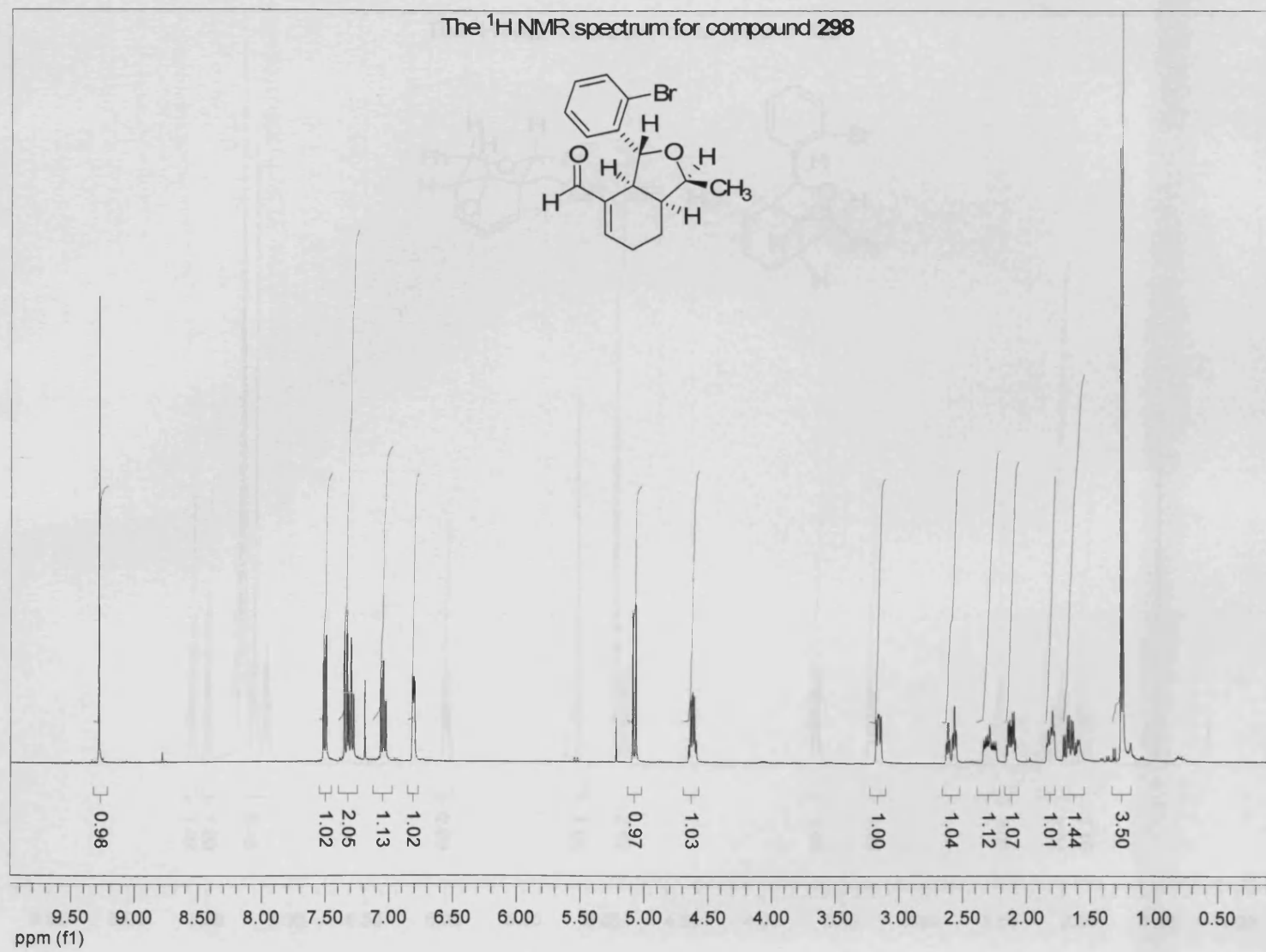
The  $^1\text{H}$  NMR spectrum for compound **237**



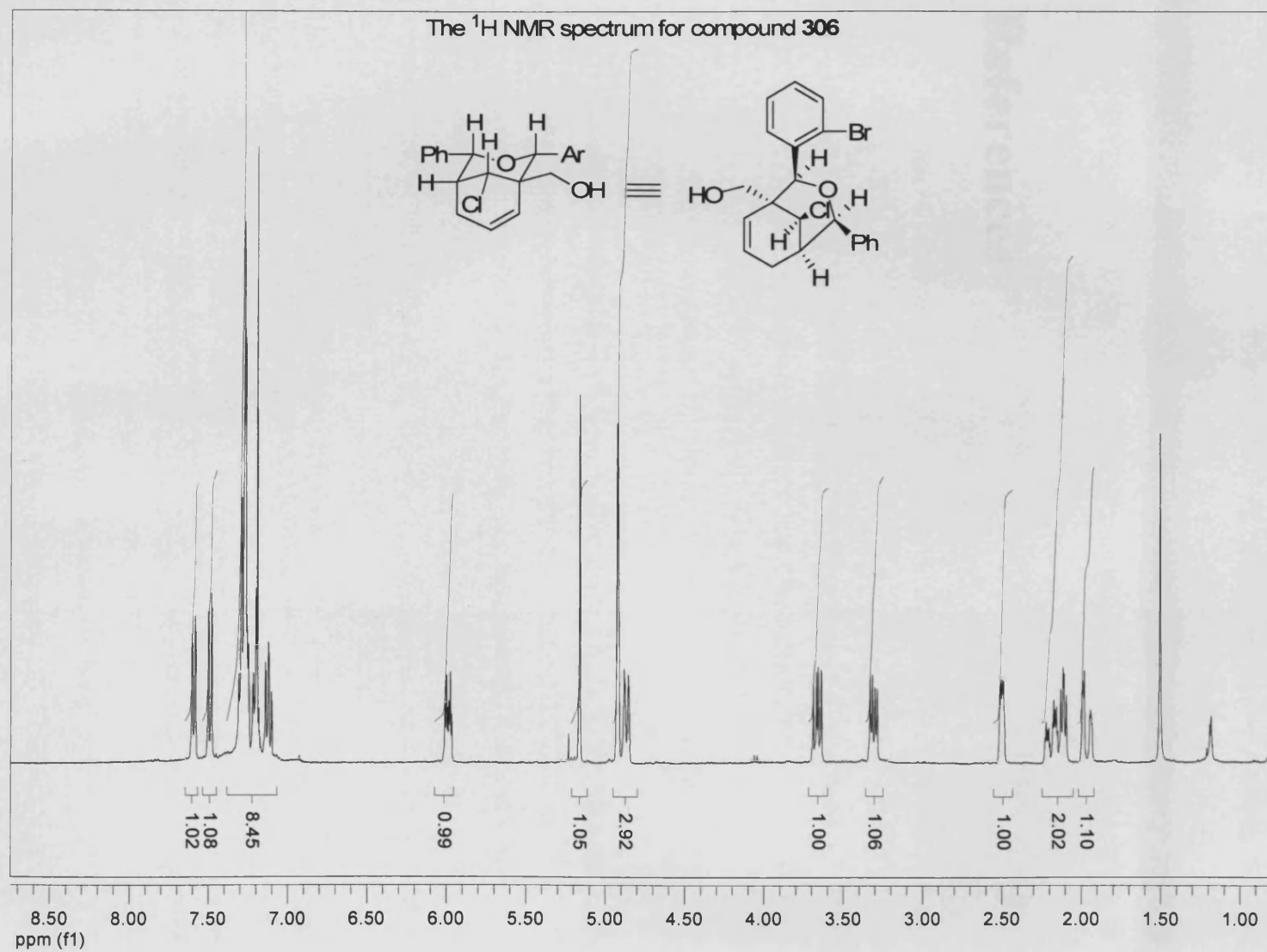
The  $^1\text{H}$  NMR spectrum for compound **248**



The  $^1\text{H}$  NMR spectrum for compound **298**



The  $^1\text{H}$  NMR spectrum for compound **306**



## References

1. Takayama, H.; Katakawa, K.; Kitajima, M.; Seki, H.; Yamaguchi, K.; Aimi, N. *Org. Lett.* **2001**, *3*, 4165.
2. (a) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (b) Christoffers, J.; Baro, A. *Quaternary Stereocentres*, Wiley-VCH, Weinheim, 2005.
3. For reviews of desymmetrisation reactions see (a) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765. (b) Abd Rahman, N.; Landais, Y. *Curr. Org. Chem.* **2002**, *6*, 1369.
4. (a) Landais, Y.; Parra-Rapado, L. *Eur. J. Org. Chem.* **2000**, *2*, 401. (b) Angellaud, R.; Babot, O.; Charvat, T.; Landais, Y. *J. Org. Chem.* **1999**, *64*, 9613.
5. Posner, G. H.; Mallamo, J. P.; Miura, K. *J. Am. Chem. Soc.* **1981**, *103*, 2886.
6. Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297.
7. Takada, H.; Nishibayashi, Y.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1511.
8. Grainger, R. S.; Tisselli, P.; Steed, J. W. *Org. Biomol. Chem.* **2004**, *2*, 151.
9. Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106.
10. Bland, D.; Hart, D. J.; Lacoutiere, S. *Tetrahedron* **1997**, *53*, 8871.
11. Bland, D.; Chambournier, G.; Dragan, V.; Hart, D. J. *Tetrahedron* **1999**, *55*, 8953.
12. Fujioka, H.; Kitagaki, S.; Ohno, N.; Kitagawa, H.; Kita, Y.; Matsumoto, K. *Tetrahedron: Asymmetry* **1994**, *5*, 333.
13. Curran, D. P.; Lin, C. H.; DeMello, N.; Junggebauer, J. *J. Am. Chem. Soc.* **1998**, *120*, 342.
14. Villar, F.; Kolly-Kovac, T.; Equey, O.; Renaud, P. *Chem. Eur. J.* **2003**, *9*, 1566.
15. Nguyen, T. M.; Seifert, R. J.; Mowrey, D. R.; Lee, D. *Org. Lett.* **2002**, *4*, 3959.
16. Curran, D. P.; Geib, S. J.; Lin, C.-H. *Tetrahedron: Asymmetry* **1994**, *5*, 199.
17. Kodama, S.; Hamashima, Y.; Nishide, K.; Node, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2659.
18. Irwin, R. L.; Smith III, H. J. *Biochem. Pharmacol.* **1960**, *3*, 147.
19. Martin, S. F.; Campbell, C. L. *J. Org. Chem.* **1988**, *53*, 3184.
20. Landais, Y.; Zekri, E. *Eur. J. Org. Chem.*, **2002**, *23*, 4037.

21. Kolb, H. C.; vanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
22. Angelaud, R.; Landais, Y. *Tetrahedron Lett.* **1997**, *38*, 1407.
23. Lorenz, J. C.; Frohn, M.; Zhou, X.; Zhang, J.-R.; Tang, Y.; Burke, C.; Shi, Y. *J. Org. Chem.* **2005**, *70*, 2904.
24. Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525.
25. Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738.
26. Ohrai, K.; Kondo; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 11737.
27. Mori, M.; Takaki, T.; Makabe, M.; Sato, Y. *Tetrahedron Lett.* **2003**, *44*, 3797.
28. Honma, M.; Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 9007.
29. (a) Studer, A.; Schleth, F. *Synlett* **2005**, 3033. (b) Studer, A.; Schleth, F. *Angew. Chem. Int. Ed.* **2004**, *43*, 313.
30. Schleth, F.; Vogler, T.; Harms, K.; Studer, A., *Chem. Eur. J.* **2004**, *10*, 4171.
31. Binmore, G.; Cardellini, L.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1997**, 757.
32. (a) Bland, D.; Chambournier, G.; Dragan, V.; Hart, D. J. *Tetrahedron* **1999**, *55*, 8953. (b) Nelson, N. A.; Fassnacht, J. H.; Piper, J. *J. Am. Chem. Soc.* **1961**, *83*, 206.
33. Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1992**, *114*, 1824.
34. Arseniyadis, S.; Yashunsky, D. V.; Dorado, M. M.; Alves, R. B.; Wang, Q.; Potier, P. *Tetrahedron* **1996**, *52*, 6215.
35. Stork, G.; Boeckmann, R. K.; Taber, D. F.; Still, W. C.; Singh, J. *J. Am. Chem. Soc.* **1979**, *101*, 7107.
36. Kenney, W. J.; Walsh, J. A.; Davenport, D. A. *J. Am. Chem. Soc.* **1961**, *83*, 4019.
37. Oppolzer, W.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 2755.
38. Ohshiro, Y.; Ando, N.; Komatsu, M.; Agawa, T. *Synthesis* **1985**, 276.
39. Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.
40. Schultz A. G.; Taveras A. G. Harrington, R. E. *Tetrahedron Lett.* **1988**, *29*, 3907.



41. Murahashi, S.; Naota, T.; Miyaguchi, N.; Noda, S. *J. Am. Chem. Soc.* **1996**, *118*, 2509.
42. (a) Schultz, A. G.; Lavieri, F. P.; Macielag, M.; Plummer, M. *J. Am. Chem. Soc.* **1987**, *109*, 3991. (b) Arseniyadis, S.; Wang, Q.; Yashunsky, D. V.; Kaoudi, T.; Alvis, R. B.; Potier, P. *Tetrahedron Lett.* **1995**, *36*, 1633; (c) Kok, P.; De Clercq, P. J.; Vandewalle, M. E. *J. Org. Chem.* **1979**, *44*, 4553. (d) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.
43. Trachtenberg, E. N.; Nelson, C. H.; Carver, J. R. *J. Org. Chem.* **1970**, *35*, 1653.
44. Posner, G. H.; Mallamo, J. P.; Hulce, M.; Frye, L. L. *J. Am. Chem. Soc.* **1982**, *104*, 4180.
45. Satoh, T.; Sakurada, J.; Ogino, Y. *Tetrahedron Lett.* **2005**, *46*, 4855.
46. Knochel, P.; Almena Perea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.
47. Volonterio, A.; Bravo, P.; Zanda, M. *Tetrahedron Lett.* **2002**, *43*, 6537.
48. Kuehne, M. E.; Lambert, B. F. *Organic Syntheses* **1963**, *43*, 22.
49. Thominiaux, C.; Chiaroni, A.; Desmaele, D. *Tetrahedron Lett.* **2002**, *43*, 4107.
50. Grethe, G.; Sereno, J.; Williams, T. H.; Uskokovic, M. R. *J. Org. Chem.*, **1983**, *48*, 5315.
51. Walker, J., Undergraduate project, Cardiff University, 2006.
52. Przewdziecka, A.; Stepanenko, W.; Wicha, J. *Tetrahedron: Asymmetry* **1999**, *10*, 1589.
53. (a) Schultz, A. G.; Fu, W. Y.; Lucci, R. D.; Kurr, B. G.; Lo, K. M.; Boxer, M. *J. Am. Chem. Soc.* **1978**, *100*, 2140. (b) Clayden, J.; McElory, A. B.; Warren, S., *J. Chem. Soc., Perkin Trans. 1* **1995**, 1913.
54. Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157.
55. Nokami, J.; Osafune, M.; Shiraishi, K.; Sumida, S.; Imai, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2947.
56. Apparao, S.; Schmidt, R. R. *Synthesis* **1987**, 896.
57. Engelhardt, U.; Linker, T. *Chem. Commun.* **2005**, 1152.
58. Bock, I.; Bornowski, H.; Ranft, A.; Theis, H. *Tetrahedron* **1990**, *46*, 1199.

59. (a) Avery, M. A.; Chong, W. K. M.; Jennings-White, C. *J. Am. Chem. Soc.* **1992**, *114*, 974. (b) Oppolzer, W.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 2755.
60. Bravo, P.; Resnati, G. *Tetrahedron Lett.*, **1985**, *26*, 5601.
61. Obringer, M.; Colobert, F.; Neugnot, B.; Solladie, G. *Org. Lett.* **2003**, *5*, 629.
62. Beckwith, A. L. J.; Lawrence, T.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 484.
63. Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893.
64. Beckwith, A. L. J.; O'Shea, D. M.; Roberts, D. H. *J. Chem. Soc., Chem. Commun.* **1983**, 1445.
65. Evans, P. A.; Manangan, T. *J. Org. Chem.* **2000**, *65*, 4523.
66. Schlosser, M.; Strunk, S. *Tetrahedron Lett.* **1984**, *25*, 741.
67. Spencer, A. *J. Organometallic Chem.* **1984**, *265*, 323.
68. Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.
69. Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290.
70. Nandi, A.; Chattopadhyay, P. *Tetrahedron Lett.* **2002**, *43*, 5977.
71. (a) Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. *J. Org. Chem.* **2001**, *66*, 5901. (b) Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. *Tetrahedron Lett.* **2000**, *41*, 9069. (c) Morita, H.; Arisaka, M.; Yoshida, N.; Kobayashi, J. *J. Org. Chem.* **2000**, *65*, 6241.
72. Chaveriat, L.; Stasik, I.; Demailly, G.; Beaupere, D. *Carbohydrate Res.* **2004**, *339*, 1817.
73. (a) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143. (b) Snider, B. B. *The Prins Reaction and Carbonyl Ene Reactions in Comprehensive Organic Synthesis*, Ed. Trost, B. M.; Fleming, I.; Heathcock, C. H., Pergamon Press, New York, 1991, vol. 2, pp. 527 – 561.
74. Hu, Y.; Skaltizky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 8679.
75. Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*, Oxford University Press, 2001, page 1140 – 1143.
76. Overman, L. E.; Pennington, L. D. *Org. Lett.* **2000**, *2*, 2683.
77. Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577.